



# Approaches to Demonstrate Bioequivalence of Narrow Therapeutic Index Drugs

*Advisory Committee for Pharmaceutical Science  
and*

*Clinical Pharmacology*

*July 26, 2011*

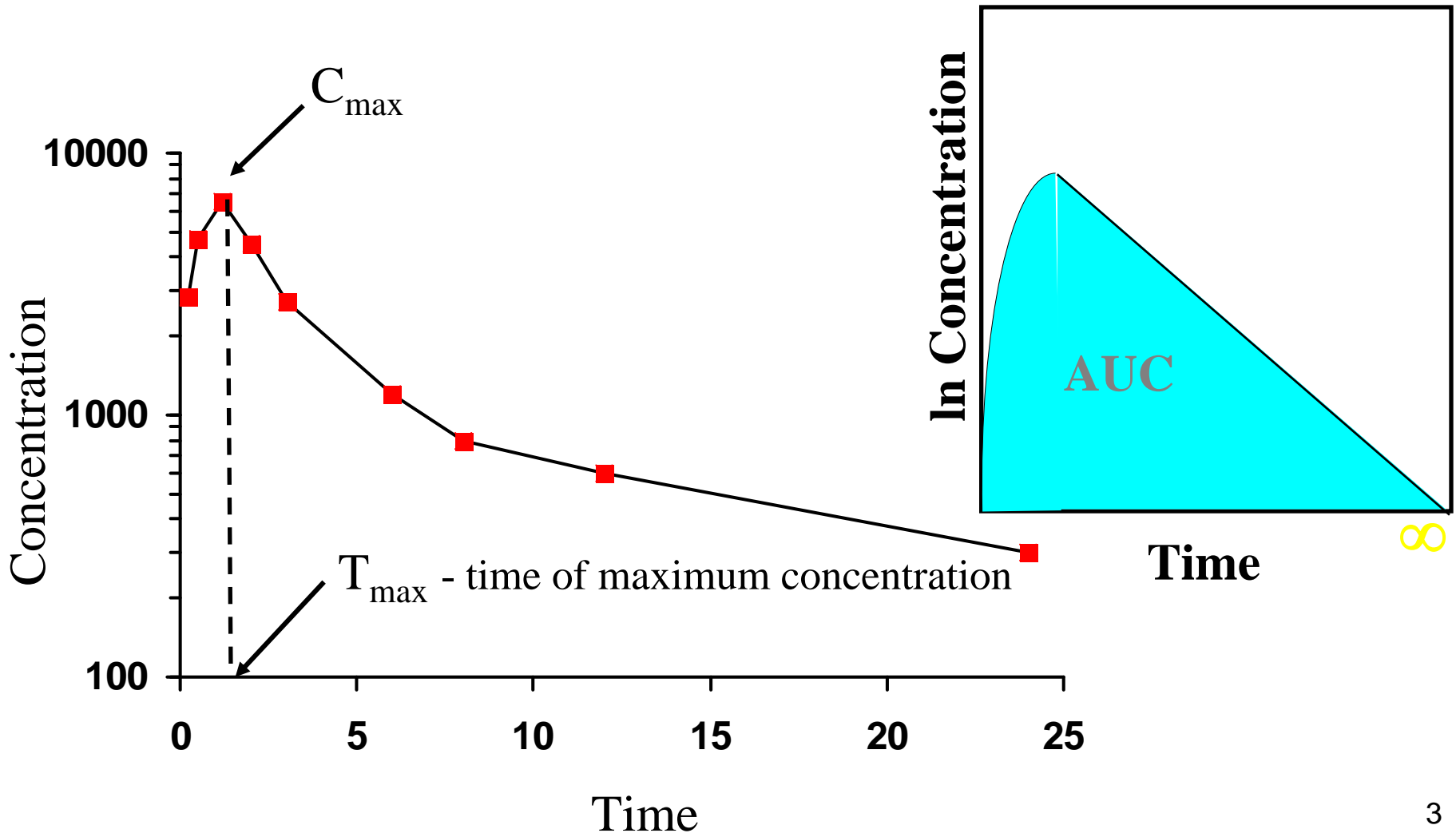
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**Lawrence X. Yu, PhD.**  
**Deputy Director for Science and Chemistry**  
**Office of Generic Drugs**

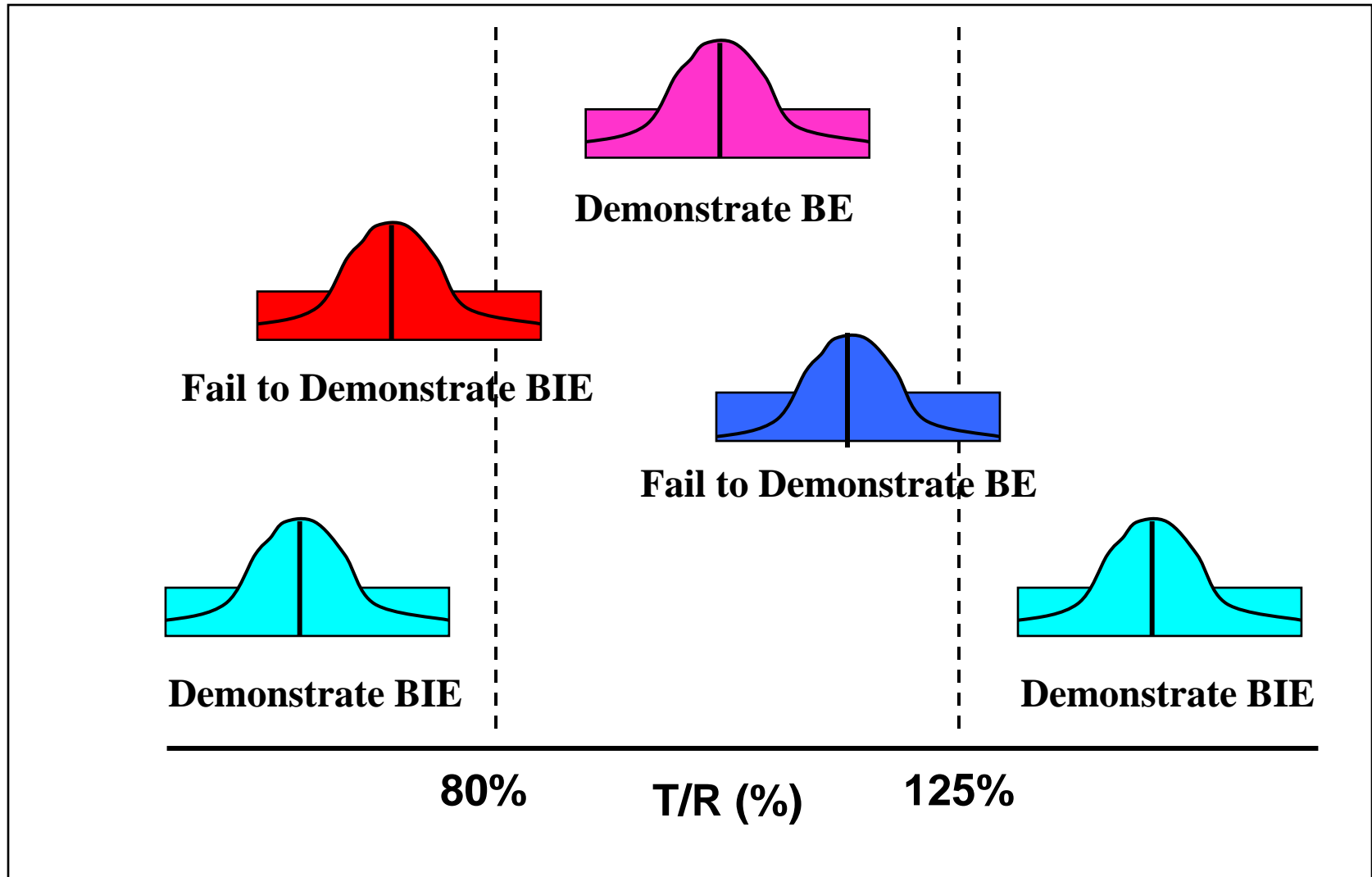
# Bioequivalence

- The absence of **a significant difference** in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study..." (21 CFR §320.1)

# Plasma Concentration Profile



# Possible Outcome of BE Studies



## Bioequivalence

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# Comparing Generic and Innovator Drugs: A Review of 12 Years of Bioequivalence Data from the United States Food and Drug Administration

Barbara M Davit, Patrick E Nwakama, Gary J Buehler, Dale P Conner, Sam H Haidar, Devvrat T Patel, Yongsheng Yang, Lawrence X Yu, and Janet Woodcock

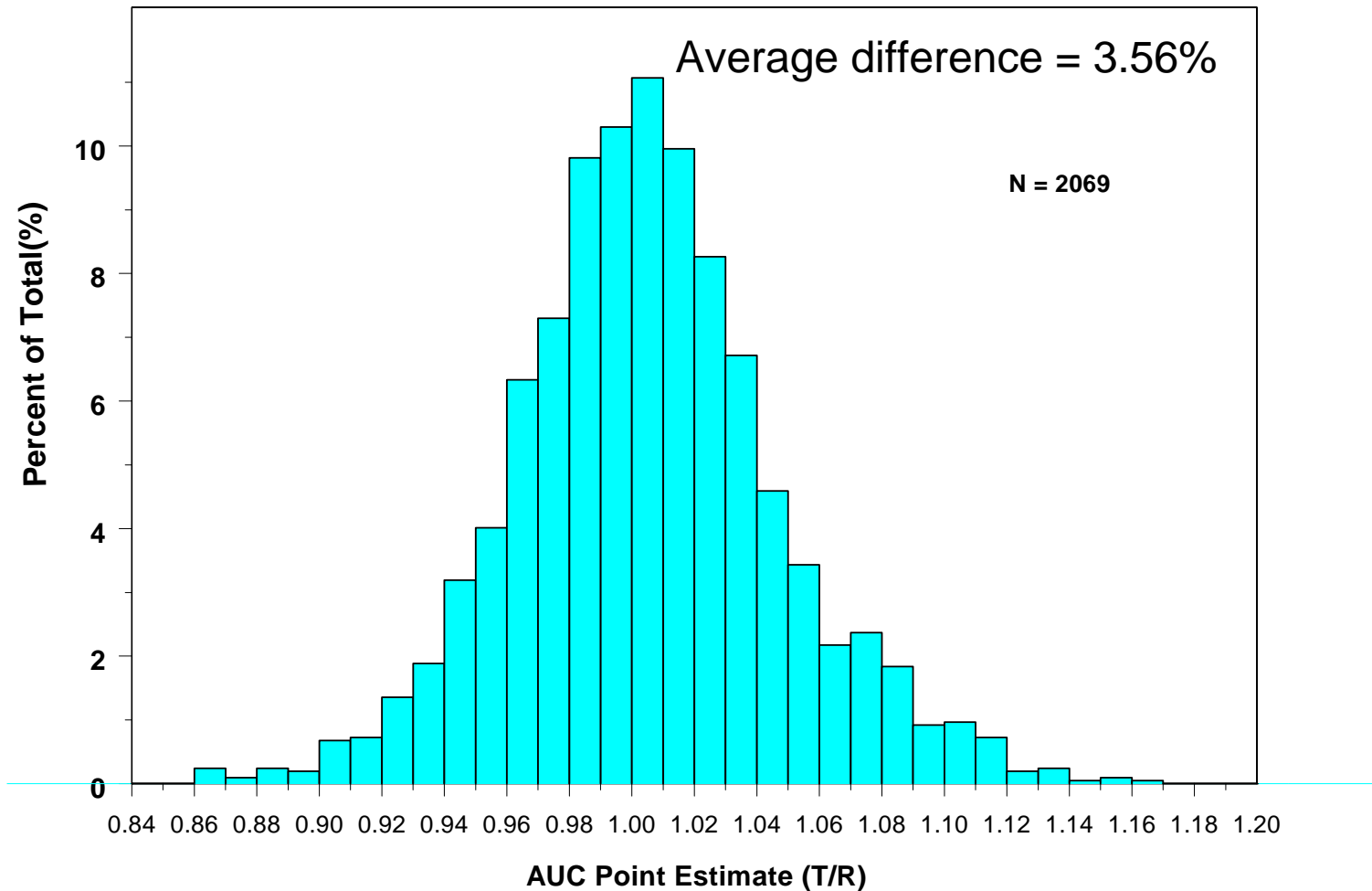
**G**eneric pharmaceutical products play a vital role in US healthcare. Since the passage of the Drug Price Competition and Patent Term Restoration Act in 1984 (Hatch-Waxman Amendments),<sup>1</sup> which set the rules under which generic drugs could compete with innovator products, the Food and Drug Administra-

**BACKGROUND:** In the US, manufacturers seeking approval to market a generic drug product must submit data demonstrating that the generic formulation provides the same rate and extent of absorption as (ie, is bioequivalent to) the innovator drug product. Thus, most orally administered generic drug products in the US are approved based on results of one or more clinical bioequivalence studies.

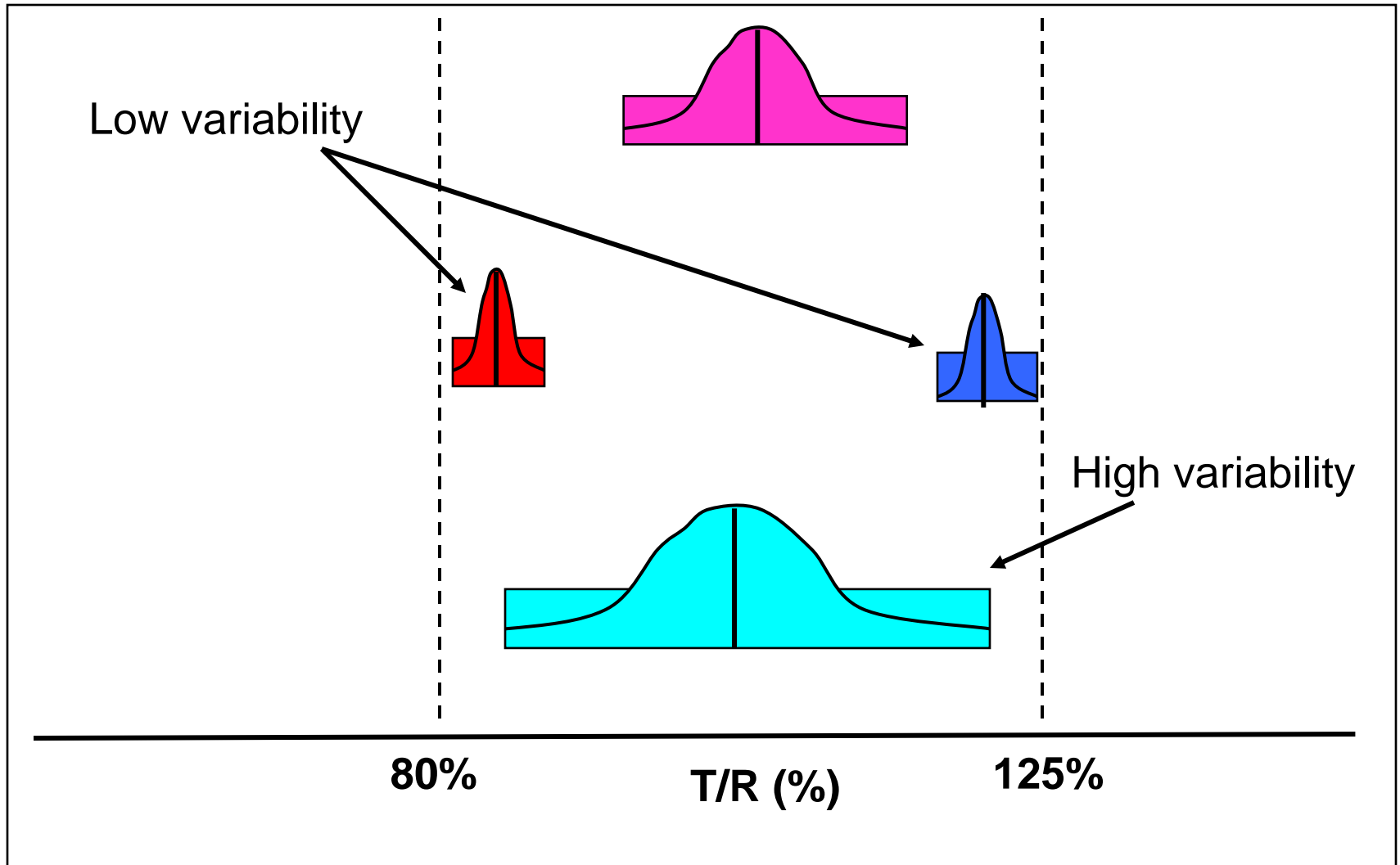
**OBJECTIVE:** To evaluate how well the bioequivalence measures of generic drugs approved in the US over a 12-year period compare with those of their corresponding innovator counterparts.

# FDA 12 Year BE Data

Distribution of  $AUC_t$  Ratios



# Effect of Variability on BE Studies



# Coefficient of Variation (CV) for NTI Drugs

Summary of Residual Variability (% CV) from ANDAs reviewed between 1996-2008

Drugs	AUC <sub>0-t</sub>		C <sub>max</sub>	
	Mean	Range	Mean	Range
Warfarin (n=29)	5.7	3.3, 11.0	12.7	7.7, 20.1
Levothyroxine (n=9)	9.3	3.8, 15.5	9.6	5.2, 18.6
Carbamazepine (n=15)	8.0	4.4, 19.4	8.7	5.2, 17.6
Lithium Carbonate (n=16)	7.8	4.5, 14.0	13.5	6.4, 24.4
Digoxin (n=5)	21.7	13.1, 32.2	21.0	14.3, 26.1
Phenytoin (n=12)	9.2	4.1, 18.6	14.9	7.4, 20.0
Theophylline (n=3)	17.9	12.8, 24.2	18.2	11.8, 25.8



## 2010 ACPS Meeting

- At the conclusion of the April 2010 ACPS meeting on NTI drugs, the Committee recommended, 13-0, that the FDA develop a list of NTI drugs with clear, specialized criteria for including drugs on the list. In addition, the committee voted 11-2 that the current bioequivalence standards are not sufficient for critical dose or NTI drugs and it was suggested that the standards need to be stricter

# 2010 ACPS Meeting (continued)

- The Committee commented:
  - Replicate studies are important
  - The Agency should look at manufacturing data on excipients from existing formularies
  - The requirements for confidence intervals should perhaps be narrower (90-111%) and should include 100% (or 1.0)
- The ACPS Committee recommended future research, including pharmacodynamic (PD) modeling and therapeutic failure causes

# FDA's Simulation Studies

- BE study design
  - Two, three, and four way crossover study designs
- BE limit
  - 80-125% and 90-111.11%
- Bioequivalence approach
  - Reference scaled average bioequivalence
  - $\sigma_{WO} = 0.10$  or  $0.25$
- Other constraints
  - Point estimate limit 5% or 10%
  - The 90% confidence interval includes 100%

# FDA's Survey on Quality and Standard

- Product design and manufacturing
- Drug assay
- Content Uniformity
- Dissolution
- Stability
- Recall
- Field Alert, MedWatch, Adverse Event Reporting System (AERS), and Drug Quality Reporting System (DQRS)

# FDA's Proposal

- Study design
- Reference-scaled average bioequivalence to compare mean
- BE limits
- Point estimate limit

# Proposed NTI Drug Definition

- Those drugs where small differences in dose or blood concentration may lead to serious therapeutic failures and/or adverse drug reactions. Serious events are those which are persistent, irreversible, slowly reversible, or life-threatening. NTI drugs generally have the following characteristics:
  - Steep dose-response curves for both safety and efficacy in the usual dosing interval or close effective concentrations and concentrations associated with serious toxicity,
  - Subject to therapeutic drug monitoring based on pharmacokinetic (PK) or pharmacodynamic (PD) measures, and
  - Generally small within subject variability.

# Today's Agenda on NTI Drugs

- Topic Introduction: BE for NTI Drug Product **Lawrence Yu**
- Narrow Therapeutic Index Drugs: An Approach to Bioequivalence and Interchangeability **Kamal K. Midha**
- Evaluation of Scaling Approaches to Demonstrate BE of NTI Drugs **Donald Schuirmann**
- Pharmaceutical Quality of NTI Drugs **Wenlei Jiang**
- FDA Proposals for NTI Drugs **Barbara M. Davit**
- Committee Discussion **Lawrence Yu**

## ACPS-CP Questions

July 26, 2011

### Bioequivalence (BE) and Quality Standards for Narrow Therapeutic Index (NTI) Drug Products

1. Is the draft definition for narrow therapeutic index (NTI) drugs, proposed by the FDA, reasonable and appropriate?
  - If not, please suggest revisions
2. Should the following be used for bioequivalence studies of NTI drugs:
  - The two-treatment, four-period, fully replicated crossover design
  - The reference-scaled average bioequivalence approach
3. Is it appropriate to tighten the assayed potency standard for NTI drugs to 95.0-105.0%?



# **Narrow Therapeutic Index Drugs: An Approach to Bioequivalence and Interchangeability**

Kamal K. Midha<sup>1</sup>, Gordon McKay<sup>1,2</sup>,  
Meir Bialer<sup>3</sup> and Maureen Rawson<sup>2</sup>

<sup>1</sup>University of Saskatchewan, College of  
Pharmacy and Nutrition, <sup>2</sup>Pharmalytics Ltd.

<sup>3</sup>The Hebrew University of Jerusalem,  
School of Pharmacy

# Outline

- Bioequivalence
  - Current practice is ABE based on 90%CI
  - Examples where current ABE approach requires change(s)
- Narrow Therapeutic Index (NTI) drugs as introduced by Dr. Lawrence Yu
- Antiepileptic drugs constitute a special class of drugs; a proposal to establish BE through scaled ABE will be presented based on Bialer and Midha, Epilepsia, 2010
- Simulations
- Discussion
- Conclusions

# Abbreviations

- BE = bioequivalence
- BEL = bioequivalence limits
- ABE = average bioequivalence
- NTIs = narrow therapeutic index drug products  
(also termed NTR or Critical Dose Drugs)
- HVD = highly variable drug ( $\text{ANOVA-CV} \geq 30\%$ )
- HVD/P = HVD or highly variable drug product
- WSV = within subject variability

# Bioequivalence and Therapeutic Equivalence

Pharmaceutical Equivalence



**Bioequivalence**



- Pharmacokinetic endpoint
- Pharmacodynamic endpoint
- Clinical endpoint
- In vitro endpoint

Therapeutic Equivalence/Interchangability

- **Bioequivalence is a surrogate for therapeutic equivalence**
- **Focus is on the documentation of bioequivalence by appropriate pharmacokinetic endpoints (in the majority of situations)**
- At present generic NTIs, once proven to be bioequivalent are regarded therapeutically interchangeable without loss of efficacy and safety.

## Conventional BE/ABE

- Typically test and reference products are administered to healthy volunteers in crossover studies and collected biological samples are assayed and subjected to PK analyses.

## Conventional BE/ABE

- Total exposure (AUC), peak exposure (C<sub>max</sub>) and time to C<sub>max</sub> (t<sub>max</sub>) are compared by analysis of variance (ANOVA) and the computed 90% confidence intervals (CI) of the geometric mean ratio (GMR) of each pharmacokinetic parameter are required to fall within 80-125% except t<sub>max</sub>.
- This approach has served us well in the majority of cases.
- However, its universal applicability has been questioned especially for HVD/P and now for NTIs and AEDs.

# Conventional ABE: 2-Treatment, 2-Period Design

- The residual mean square in ANOVA contains several variance components:
  - Within subject variability in absorption, distribution, metabolism and elimination (plus an element of analytical variability )
  - Within formulation variability
  - Subject by formulation interaction
  - Random unexplained variation

## Conventional ABE: 2-Treatment, 2-Period Design

- In a 2-treatment, 2-period design, the components of the residual mean square arising from ANOVA cannot be separated (therefore we will not know if the variance of test and reference products are similar or different).
- The residual mean square is used...
  - In the calculation of the ANOVA-CV (an estimate of within subject variability but confounded)
  - In the calculation of the 90%CI



# The 90% Confidence Interval

- In ABE based on 2-treatment, 2-period designs, the width of the 90% confidence interval depends on...
  - The magnitude of the ANOVA-CV
  - The number of subjects in each sequence

## Issues concerning interchangeability (switchability) for NTIs; How can we alleviate the issues?

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- For NTIs therapeutic issues can arise when a patient is maintained on brand itself (within brand or between two lots of a brand) or is switched from a brand to a generic as well as from one generic to another generic. This suggests that PK variability (within brand, within generic, between brand and generic and between generic1 and generic2) may be the root cause of therapeutic failure. We need to correct this situation as much as possible.

## Issues concerning interchangeability (switchability) for NTIs; How can we alleviate the issues?

- Clearly PK variability ( $WSV$ ) observed within the brand product and lots of the brand is at present operational and accepted. Therefore our efforts should be directed that PK variability within the generic product(s) ( $WSV_T$ ) and between generic and brand should be equal or no greater than what we observe for the brand to brand ( $WSV_R$ ).

# Number of Generics for two NTIs in the market

**Table 1** Number of generic manufacturers of carbamazepine and phenytoin

Brand name, dose	Generic name	Number of Generic Manufacturers
Dilantin, 100mg	phenytoin sodium	7
Tegretol, 200mg	carbamazepine	6

Adapted from Megan Barrett, J.Amer.Acad.Nurse Prac., 22, 300-304, 2010

# A Case Reports of Generic Substitution for two NTIs

## NTIs used by patients in Case Reports

AED before switch	N	AED at time of seizure	n
Dilantin Phenytek	14 1	Phenytoin	15
Tegretol Carbetrol Tegretol XR	5 1 1	Carbamazepine	7

- Therefore clinicians and patients are reluctant to switch to generics.

Adapted from: Berg et al, 2008, Neurology 71 525-530

# **An ABE approach to reduce therapeutic risk due to PK variability**

*Epilepsia*, 5 (6), 941-950, 2010

## **CRITICAL REVIEW AND INVITED COMMENTARY**

### **Generic products of antiepileptic drugs: A perspective on bioequivalence and interchangeability**

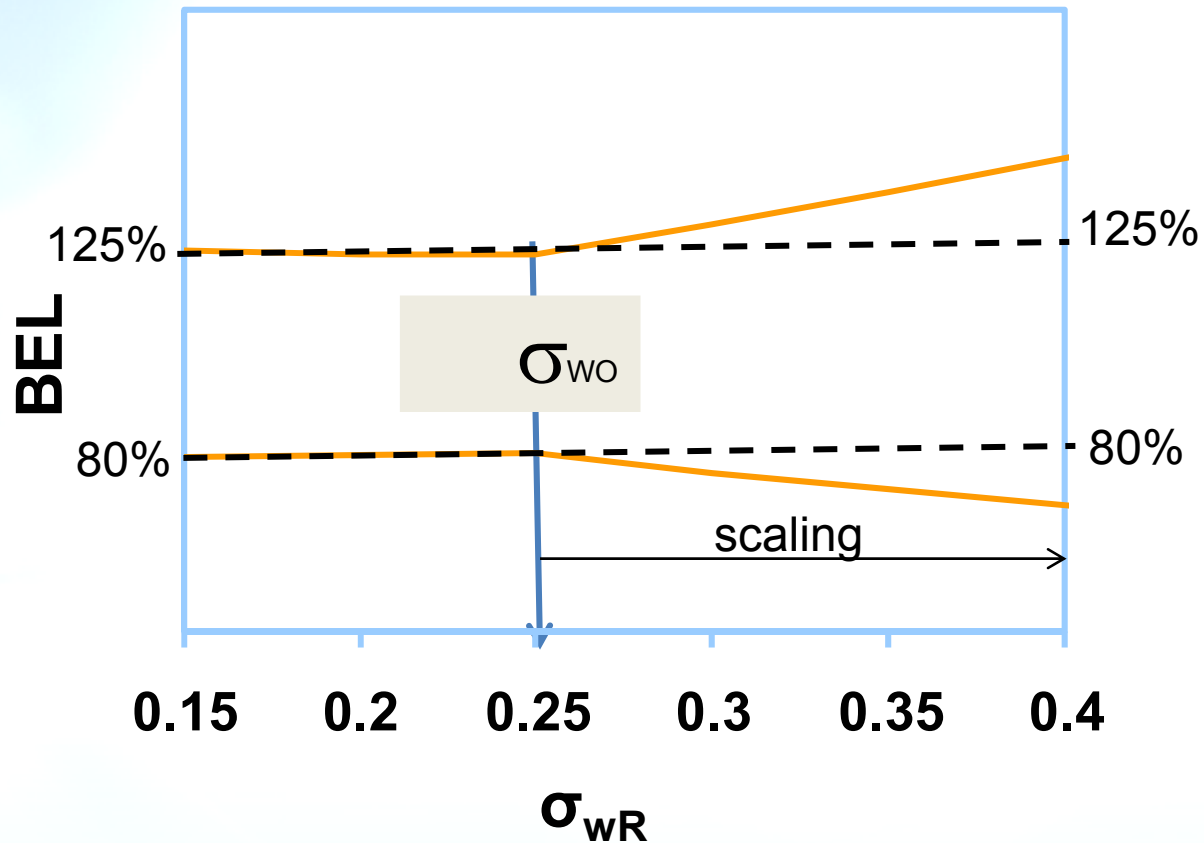
**Meir Bialer and Kamal K. Midha**

- We propose a scaled average bioequivalence approach that will ensure that fluctuations in plasma levels are no greater than those experienced within the brand reference product.

# What Is Scaled Average Bioequivalence (sABE)

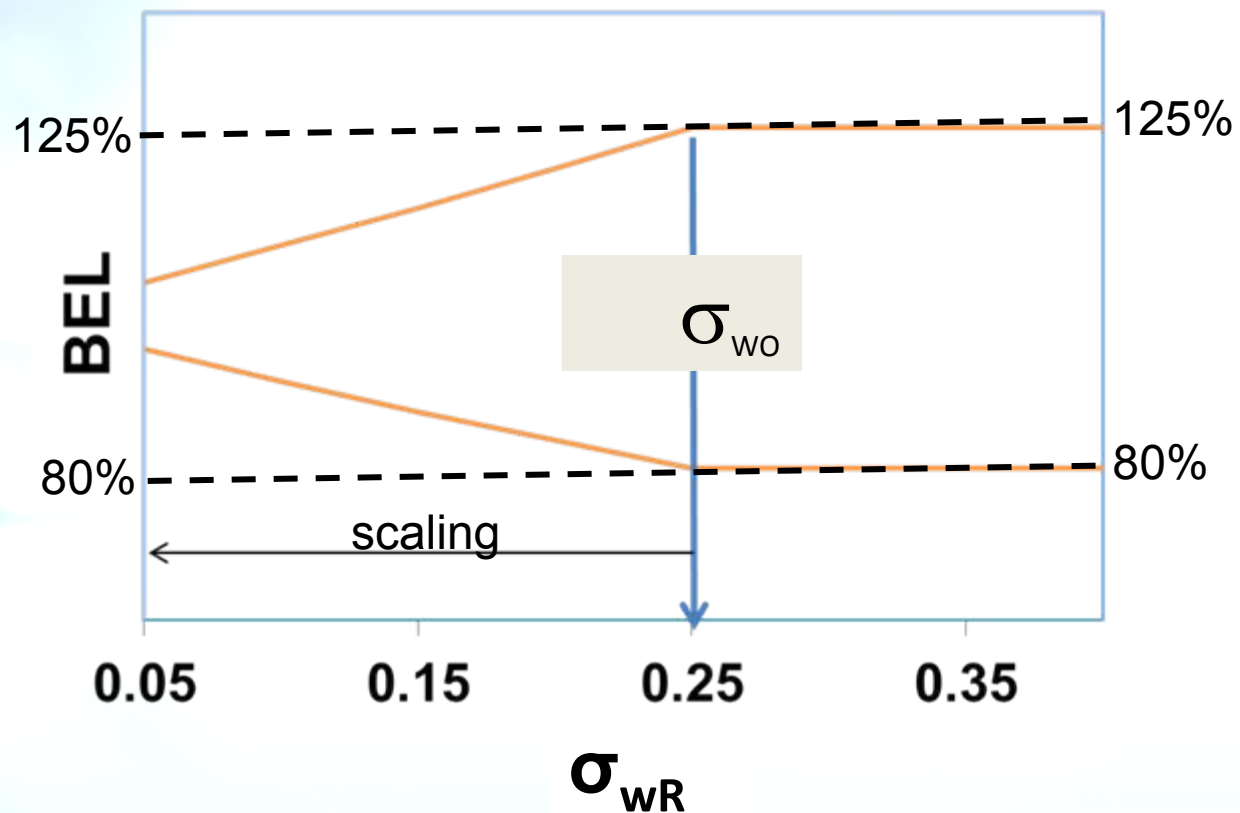
- sABE is an approach in which ABE is scaled based on a variance component.
- The most recent and highly cited example is sABE for highly variable drugs.
- The BE Limits are scaled based on reference to reference variance from a replicate design study. Alternately the kinetic parameters obtained within a BE study may be scaled using the same variance just mentioned.

# A pictorial representation of scaling in BE for HVDs





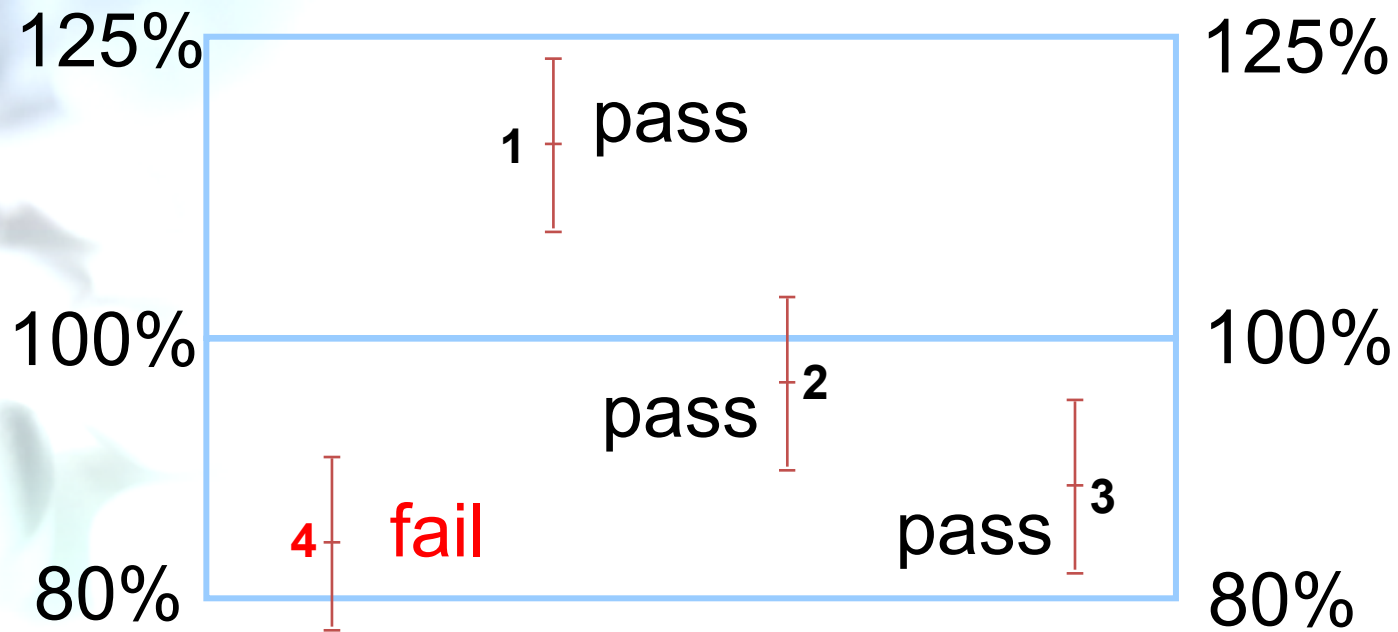
# A pictorial representation of scaling in BE for NTIs



# ANOVA-CV and its interplay with point estimates and the 90% CI

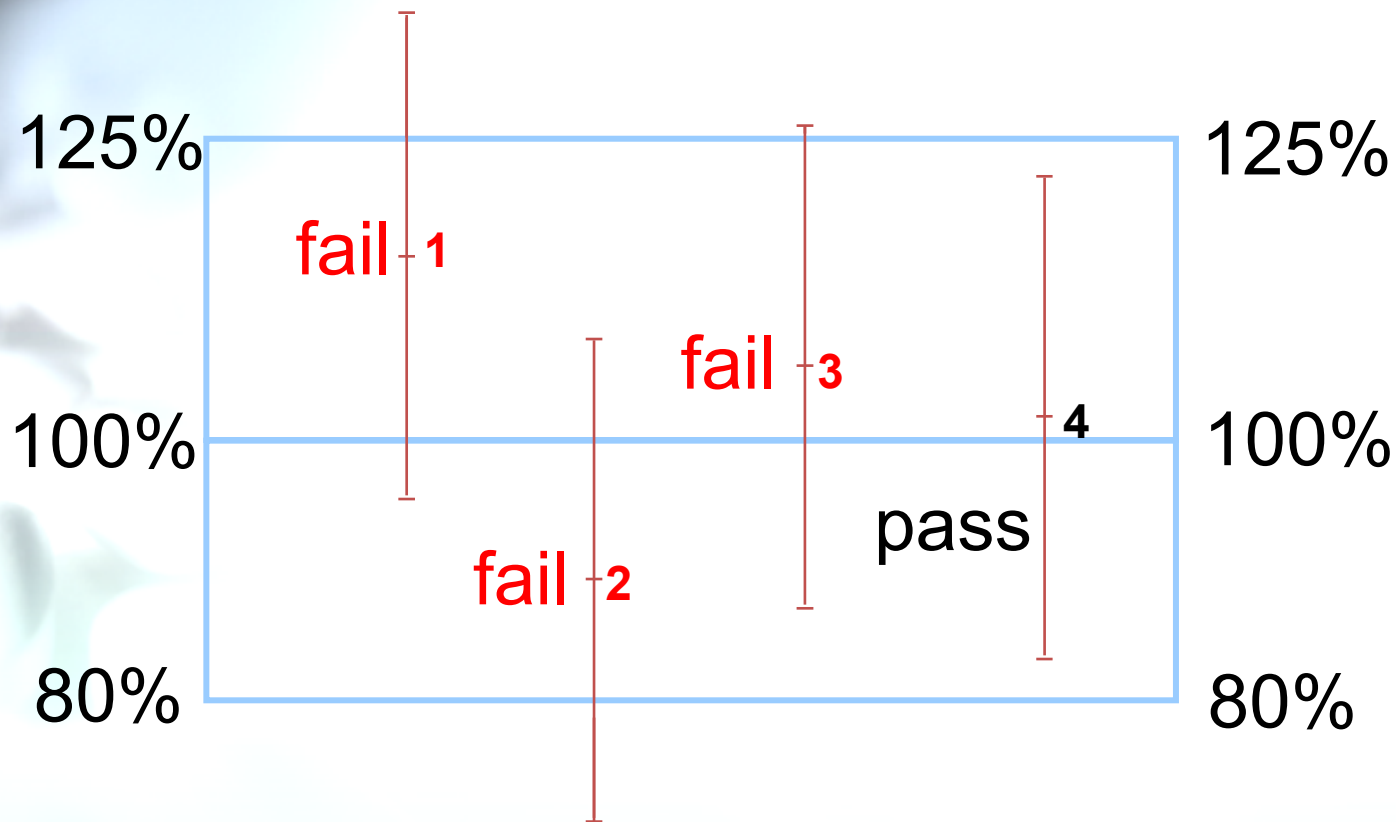
- The following 2 slides depict confidence intervals in 4 BE studies in which the width of the 90% CI is the same, but the GMR (point estimate) varies
- Traditional ABE: 2-treatment, 2-period design
- A low variability drug ANOVA-CV 14%
- A high variability drug ANOVA-CV 43%

## ANOVA-CV 14%, 24 subjects



GMR may deviate a long way from 100%

## ANOVA-CV 43%, 37 subjects



GMR must be close to 100% to fit in BE limits

# Replicate Designs

- Both 3 and 4 period replicate designs are possible. In the case of 3 period design (HVDs) only the reference is replicated.
- In 4 period replicate designs, the Test and Ref products are both replicated.

# Replicate Designs

- We propose doing a true replicate design employing:
  - 4-period, 2-sequence designs
    - e.g., TRTR and RTRT (where T & R represent the test and reference formulations)
    - Statisticians encourage the use of only two sequences to avoid compounding sequence effects

# Advantages of Replicate Designs

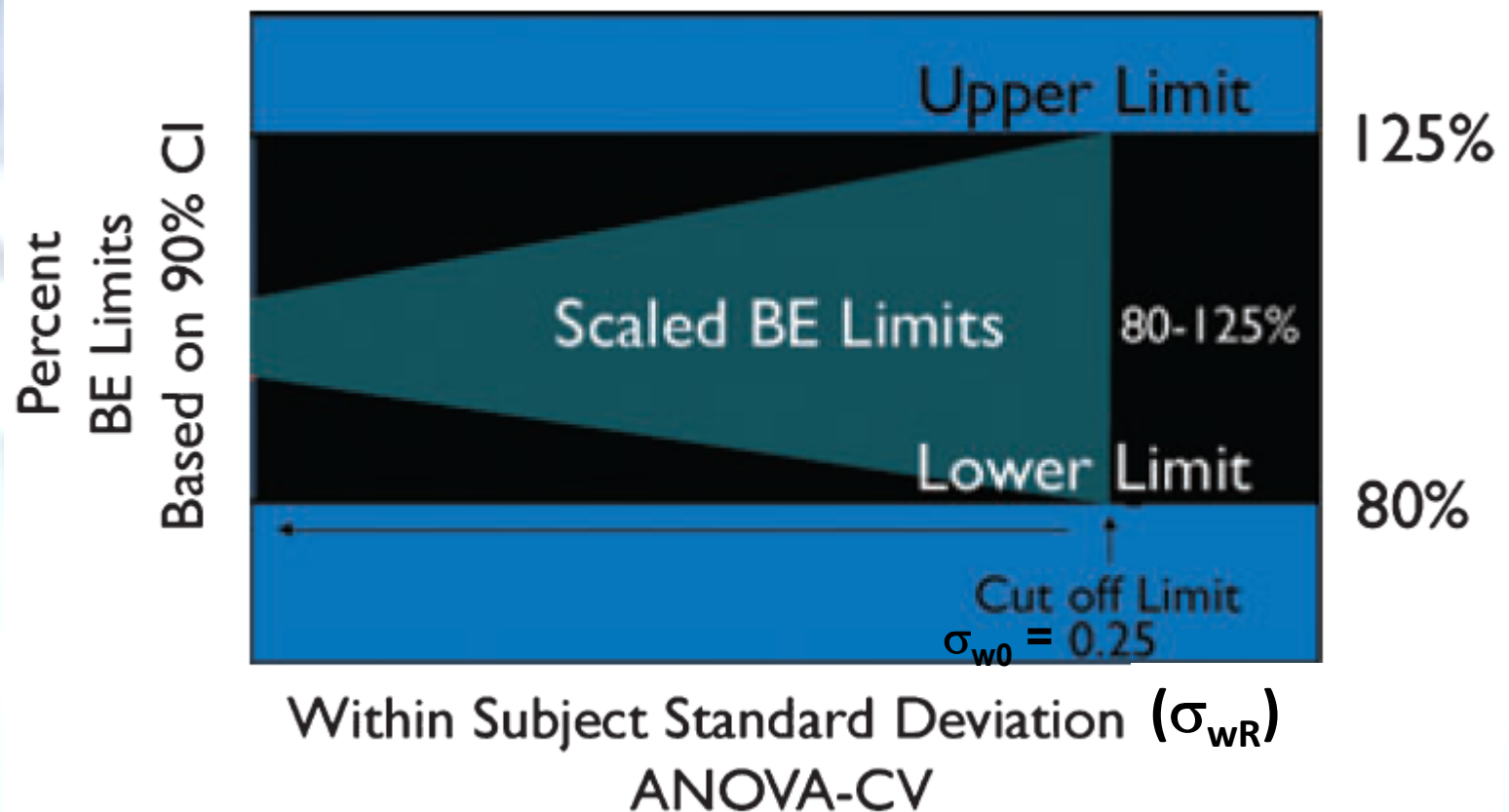
- Permits separate estimation of the variance associated with the test and ref formulations (Test vs Test and Ref vs Ref)
- This facilitates a better understanding of the pharmaceutical quality of the Test and Ref formulations which is based on the magnitude of the variance – larger the variance the poorer the pharmaceutical quality of the product.

# Advantages of Replicate Designs

- Ideally the test product should not be of poorer pharmaceutical quality than the reference product. It means that the magnitude of the Test to Test variance should not be greater than that of the Ref to Ref variance, if at all variance value should be less than the Ref to Ref variance.



## Reference sABE for AEDs/NTIs



## Ref scaled ABE by scaling the BEL

- The BE Limits based on the reference to reference WSV are scaled using the following formula:

$$\text{BEL} = \exp \left[ \frac{\pm (\ln 1.25) \sigma_{wR}}{\sigma_{w0}} \right]$$

# Simulations

- USFDA has suggested a reference scaled regulatory criteria for determination of reference scaled individual bioequivalence (1)
- Simulations were performed using previously published methodology which has been adapted for sABE four period two sequence designs (2).
- Simulations assumed a true within subject CV of the reference product,  $\sigma_{wR}$  at three levels, 6, 12 and 22%.

1. USFDA, Statistical approaches to establishing bioequivalence-guidance for industry, CDER, 2001
2. Tothfalusi et al, Pharm. Res., 18, 728-733, 2001

# Simulations

- The between subject variance and the variance for the test were set equal to that of the reference.
- Each study had 24 subjects, the true GMR (T/R%) was gradually increased from 100% until no further studies were acceptable.
- 500 simulations were performed under each selected condition detailed above.

## Simulations cont'd

- The number of studies which met acceptance criteria based on traditional unscaled ABE and sABE with  $\sigma_{w0}=0.2$  and 0.25 were examined.
- 90% CIs were calculated by an adaptation of Hyslop et al, 2000.
- For each simulation the true GMR was plotted against the % of studies that met the acceptance criteria.

Hyslop et al, Stat. Med., 19, 2885-2897, 2000

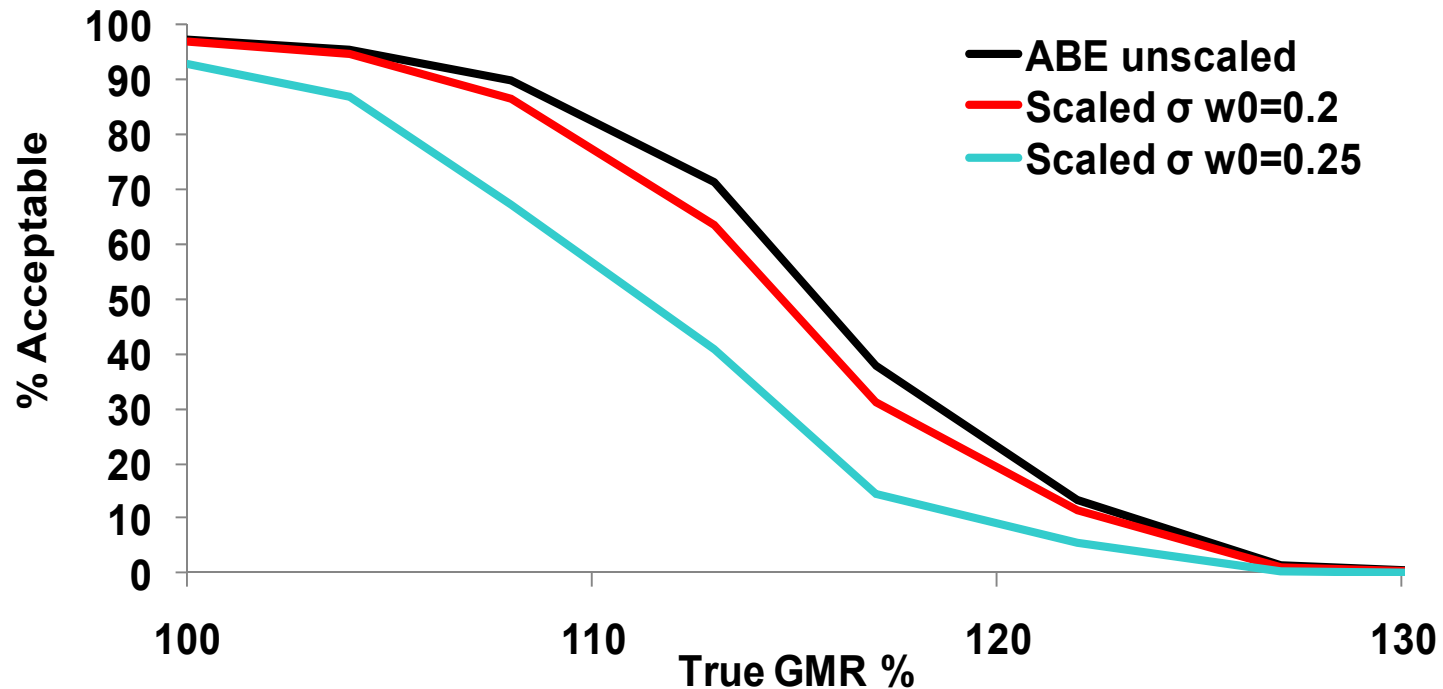
## Referenced scaled ABE applied to the 90% confidence intervals

- 24 Subject, 4 period, 2 sequence studies were simulated
- Scaled ABE - 
$$\frac{(\mu_T - \mu_R)^2}{\sigma_{WR}^2} \leq \frac{(\ln(1.25))^2}{\sigma_{w0}^2}$$
- Rearranged as - 
$$(\mu_T - \mu_R)^2 - \sigma_{WR}^2 \left[ \frac{(\ln(1.25))^2}{\sigma_{w0}^2} \right] \leq 0$$
- An adaptation of Hyslop et al was used to calculate the upper CI, based on t-test as usual for the first term and  $\chi^2$  test for the variance term

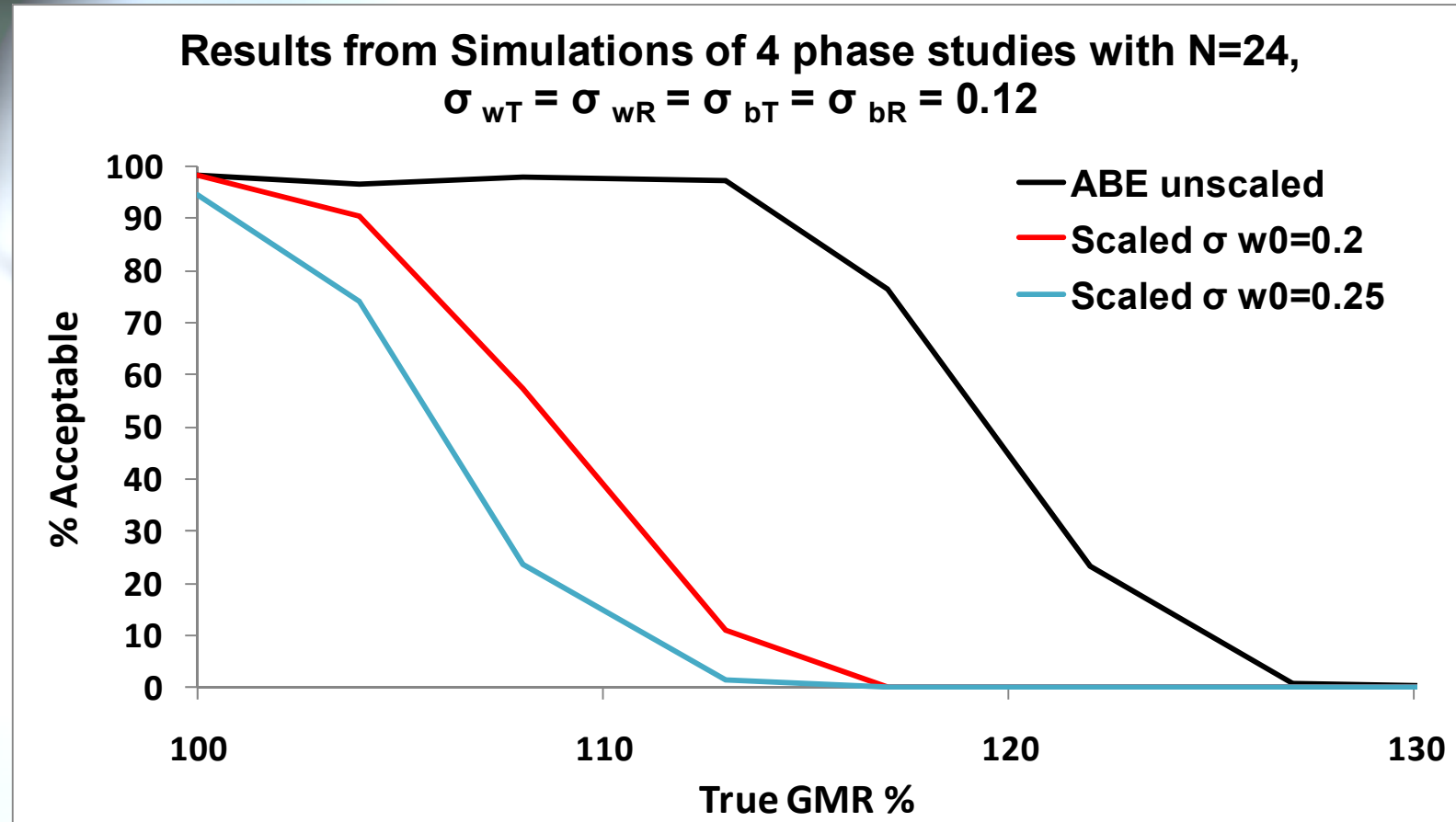
Hyslop et al, Stat. Med., 19, 2885-2897, 2000

# Power Analysis $\sigma_{wR} = 0.22$

Results from Simulations of 4 phase studies with N=24,  
 $\sigma_{wT} = \sigma_{wR} = \sigma_{bT} = \sigma_{bR} = 0.22$

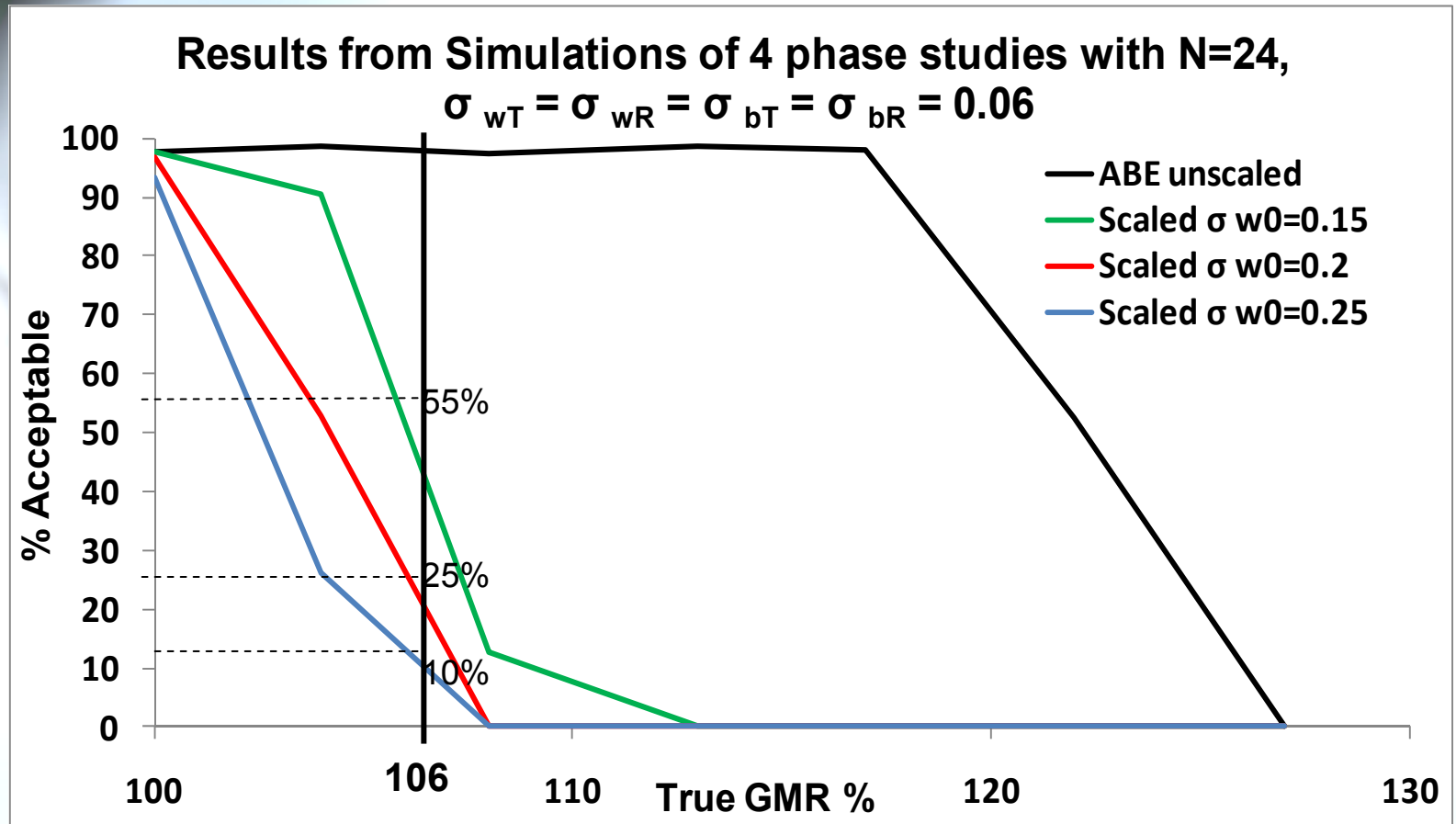


# Power Analysis $\sigma_{wR} = 0.12$

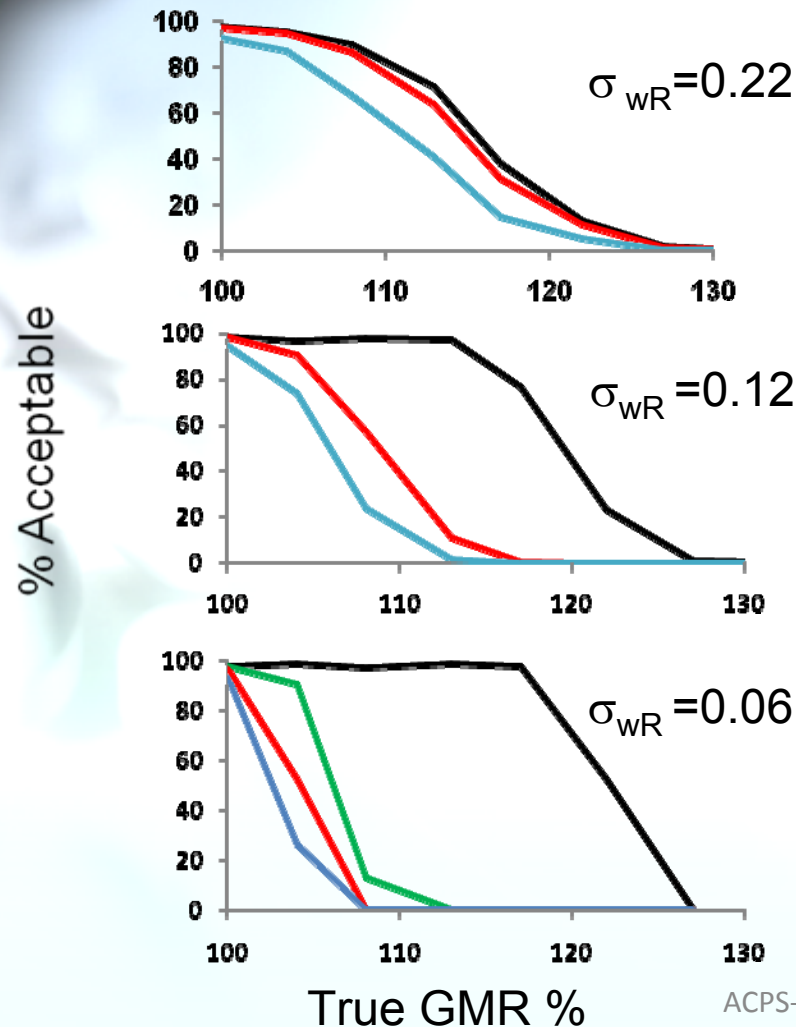




# Power Analysis $\sigma_{wR} = 0.06$

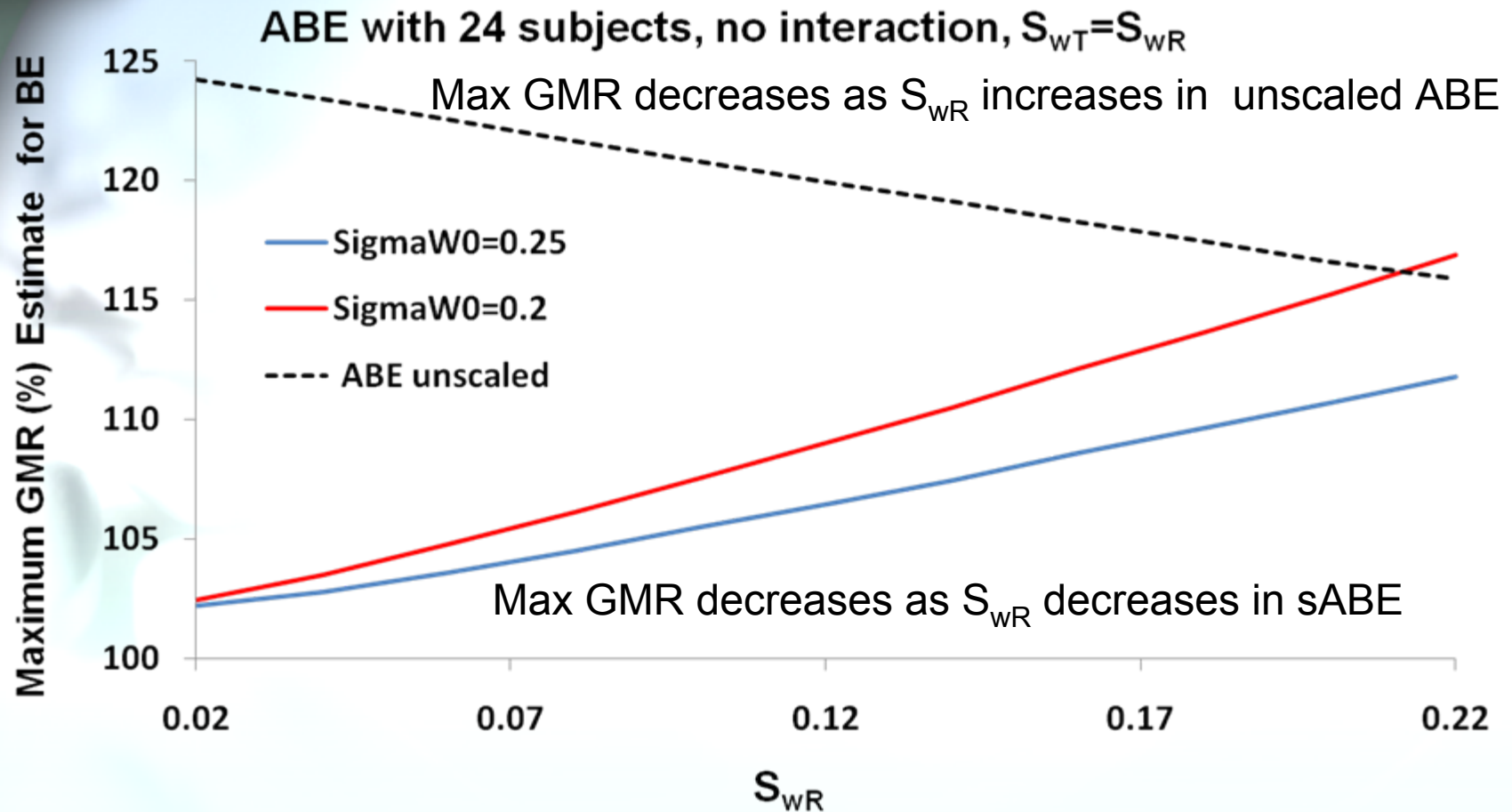


# The influence of $\sigma_{wR}$ on Scaling and its interplay with the maximum allowable GMR



- Scaling with ref to ref variability with a judiciously selected value for  $\sigma_{w0}$ , has a profound influence in controlling the BE outcome.
- It can restrain the 90% CI to give tighter BE Limits.
- In addition it can control the deviation of GMR from the ideal of 100%

# Maximum GMR allowable



# Conclusions

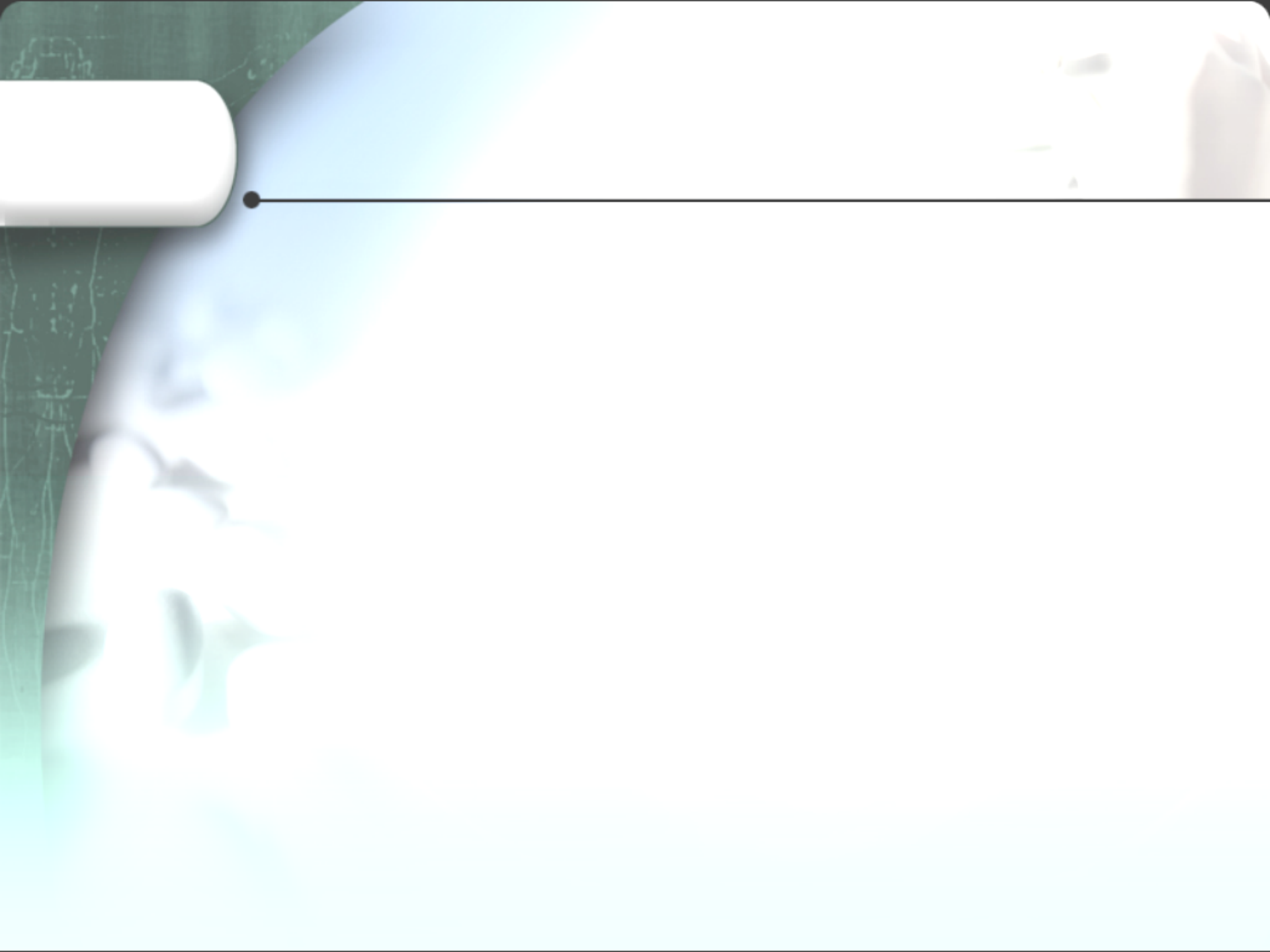
- We propose 4-Period two sequence designs in which both Test and Ref are replicated for NTIs and sABE using Ref to Ref variance.
- Replicate designs will provide separate estimates of Test vs Test and Ref vs Ref variances which will allow us to assess the pharmaceutical quality of each of the formulations.

## Conclusions

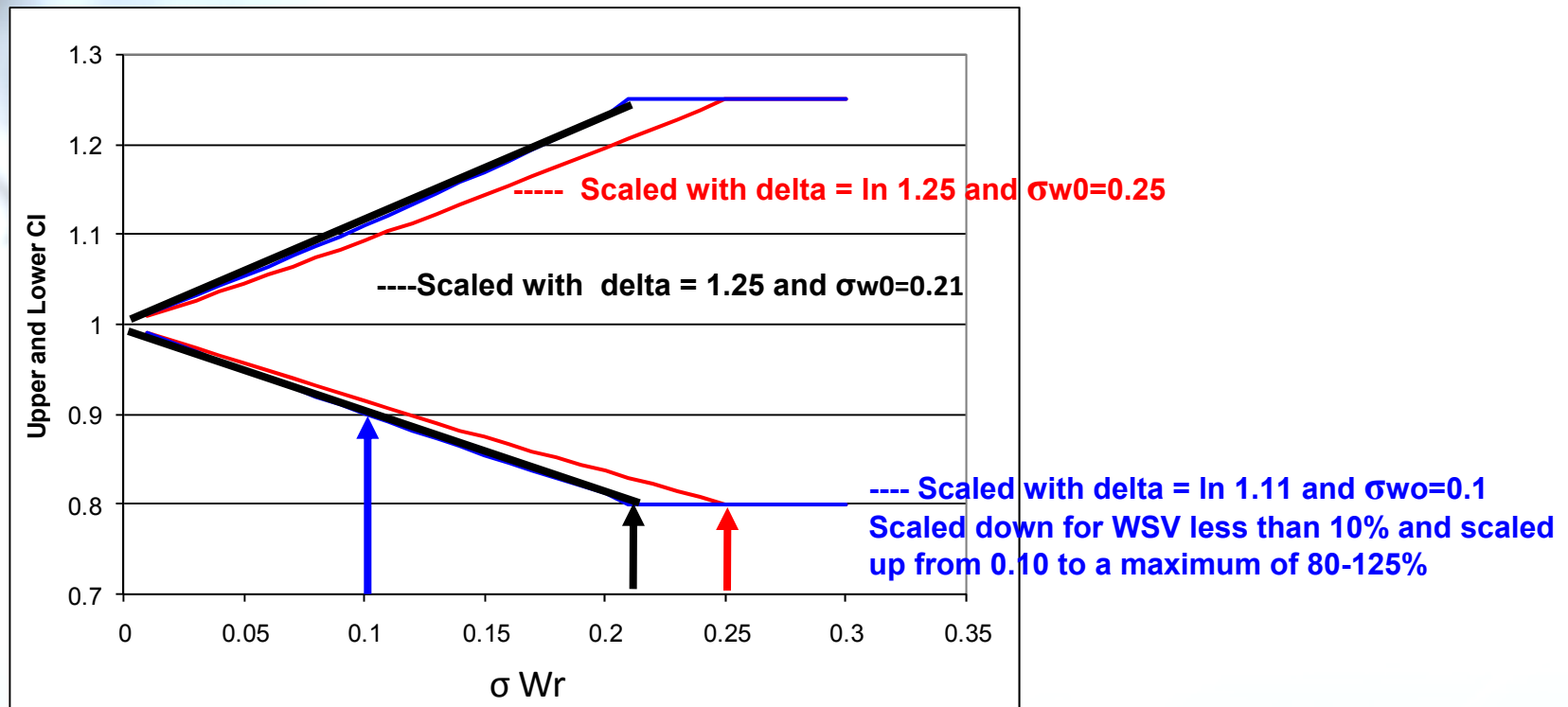
- We also propose that Test to Test variance should be less than or not significantly different than the Ref to Ref variability (F-test or equivalent)
- Ideally we propose that 2 lots of each the Test and Ref product be tested in the 4-period replicate study.

# Conclusions

- In our opinion there is no need to add additional constraints around the point estimate since the WSV will in itself limit the maximal allowable GMR in the final analysis.
- We believe the issues related to switchability between brand-bioequivalent generics (generic1 and generic2) can be minimized by constraining the 90%CI to include 100%.



## Conventional sABE versus BEL re-defined and scaling up and down from that limit based on WSV







# Evaluation of Scaling Approaches to Demonstrate BE of NTI Drugs – OGD Simulation Efforts

*Advisory Committee for Pharmaceutical Science  
and*

*Clinical Pharmacology*

*July 26, 2011*

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**Donald J. Schuirmann**  
**Expert Mathematical Statistician**  
**Office of Biostatistics, OTS, CDER**

# Simulation Effort

The Office of Generic Drugs (OGD) Working Group, in collaboration with members of the Office of Biostatistics, carried out extensive simulations to investigate the properties of various approaches to bioequivalence (BE) assessment for Narrow Therapeutic Index (NTI) drug products.

## Simulation Effort (cont'd.)

- log-transformed PK endpoints (i.e.  $\ln(\text{AUC})$  and  $\ln(\text{Cmax})$ ) were assumed to be normally distributed
- $\mu_R$  and  $\mu_T$  are the population means for the Reference product (i.e. the RLD) and Test product (i.e. the proposed generic) log endpoints. The performance of the approaches considered depends on  $\mu_T - \mu_R$ , which is the log of the Geometric Mean Ratio (GMR.)

## Simulation Effort (cont'd.)

- Within-subject standard deviations for the log-transformed endpoints, for the Reference and Test products and denoted  $\sigma_{WR}$  and  $\sigma_{WT}$  respectively, may differ.
- The within-subject standard deviation ( $\sigma$ ) for the log-transformed endpoint is related to the within-subject coefficient of variation (CV) for the untransformed endpoint by the formulae

$$CV = \sqrt{e^{\sigma^2} - 1} \quad \text{or} \quad \sigma = \sqrt{\ln(1 + CV^2)}$$

## Simulation Effort (cont'd.)

- A more complete description of the assumed statistical model may be found in the January 2001 CDER guidance document *Guidance for Industry - Statistical Approaches to Establishing Bioequivalence*
- The parameter  $\sigma_D$  (described in the January 2001 Guidance) was assumed equal to zero in all simulations. However, the effect of having  $\sigma_D > 0$  is similar in many cases to having  $\sigma_{WT} > \sigma_{WR}$ , which we did consider

## Simulation Effort (cont'd.)

- Simulations were carried out in the *S-Plus*, *R*, or *APL* computer programming languages
- Each estimated probability based on one million (1,000,000) simulated studies

# Approaches Considered

- Scaled Average BE
- Regular Unscaled Average BE, but with tighter limits – 90-111.11% instead of 80-125%
- Point Estimate Constraints (PEC) in addition to the above
- Requiring the usual 90% confidence interval to contain 1.0

## NTI Drugs Show a Range of Variability

Residual Variability (% CV) from ANDAs reviewed between 1996-2008				
	AUC <sub>0-t</sub>		Cmax	
Drugs	Mean	Range	Mean	Range
Warfarin (n=29)	5.7	3.3 , 11.0	12.7	7.7 , 20.1
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Theophylline (n=3)	17.9	12.8 , 24.2	18.2	11.8 , 25.8

Not a comprehensive list of NTI drugs



# Scaled Average BE

- scaled average BE criterion

$$\frac{(\mu_T - \mu_R)^2}{\sigma_{WR}^2} \leq \theta$$

- $\theta$  defined as

$$\theta = \frac{[\ln(\Delta)]^2}{\sigma_{W0}^2}$$

$\sigma_{W0}$  is a regulatory constant.  $\Delta$  is the upper BE limit (e.g. 1.25) that applies when  $\sigma_{WR} = \sigma_{W0}$

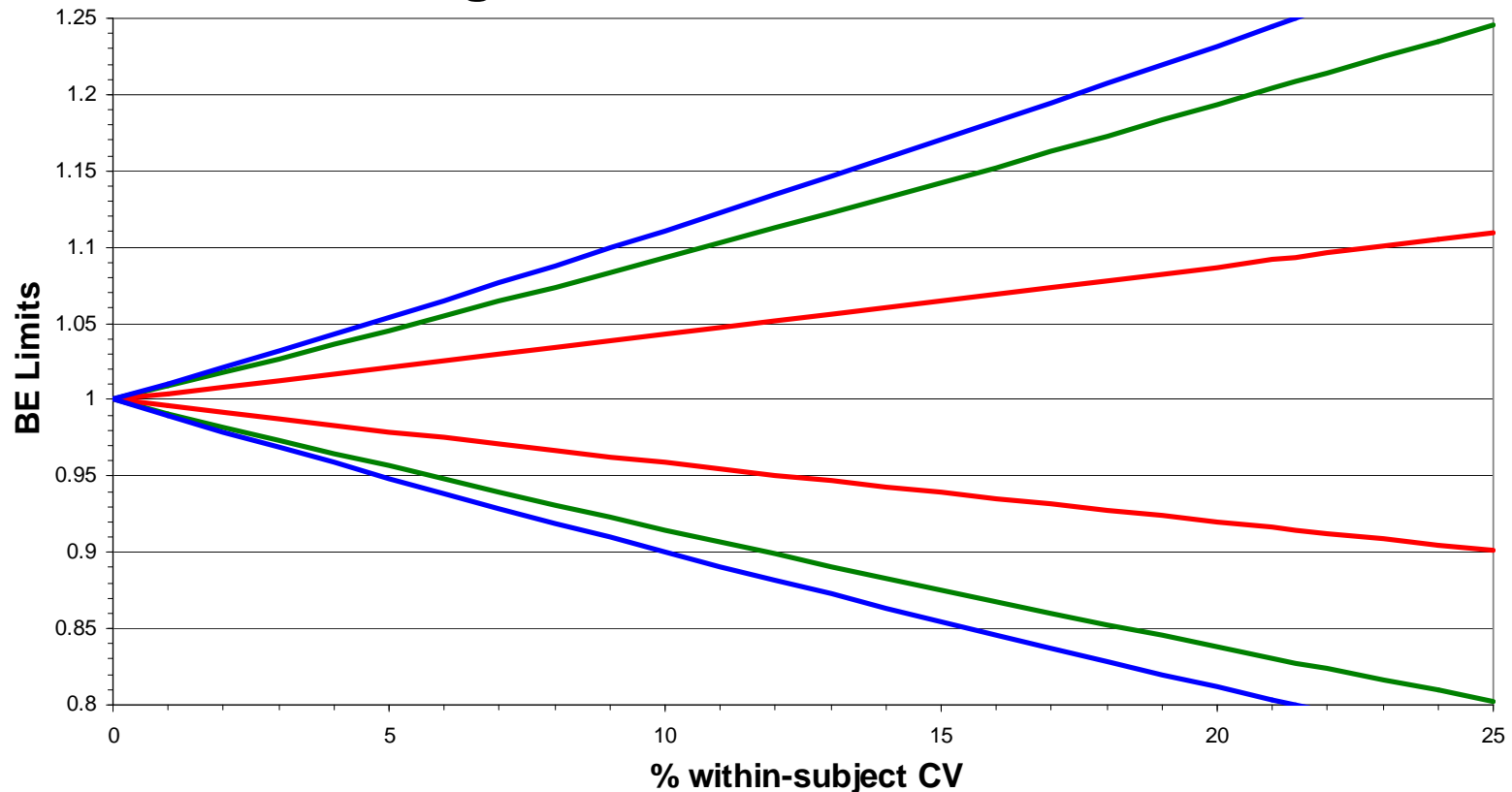
## Scaled Average BE (cont'd.)

The OGD Working Group considered three cases

- Case 1:  $\Delta = 1.25$   $\sigma_{W0} = 0.25$   
(same as currently used for highly variable drugs)
- Case 2:  $\Delta = 1.11111$   $\sigma_{W0} = 0.25$   
(note  $1.11111 = 1/0.9$ )
- Case 3:  $\Delta = 1.11111$   $\sigma_{W0} = 0.10$

# Scaled Average BE (cont'd.)

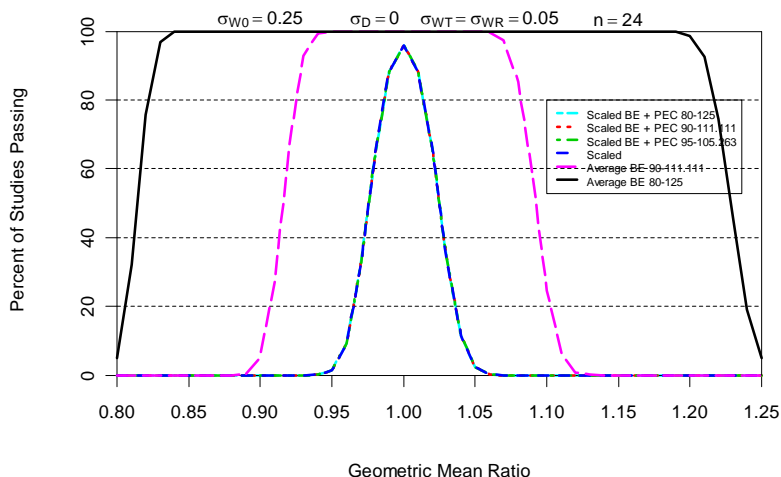
implied BE limits for three cases  
Case 1=green Case 2=red Case 3=blue



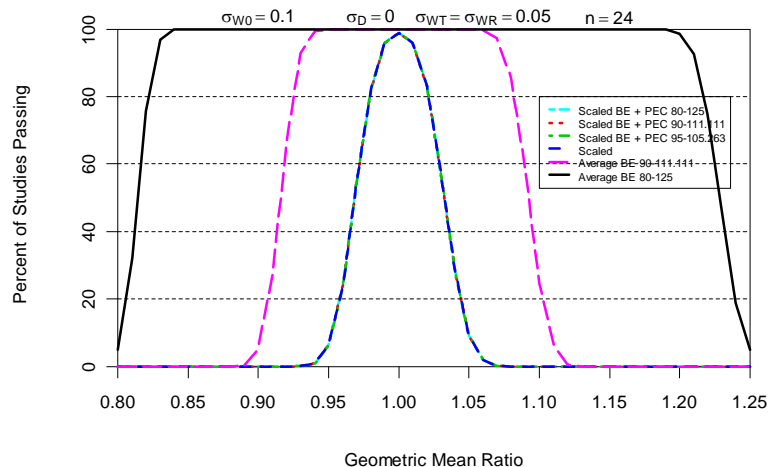
# Scaled Average BE (cont'd.)

- It became apparent that Case 2 was too stringent
- Results for Case 1 and Case 3 were qualitatively similar. Case 1 is slightly more stringent than Case 3.

Percent of Studies Passing Pure Scaled BE Test with Point Estimate Constraint and Average BE for 4-Way Cross-Over Studies with



Percent of Studies Passing Pure Scaled BE Test with Point Estimate Constraint and Average BE for 4-Way Cross-Over Studies with



# Point Estimate Constraints

Point Estimate Constraints (PEC) considered

- 95-105.26%
- 90-111.11%
- 80-125%

For the range of variabilities considered, 80-125% had no effect (i.e. it wasn't any harder to pass with it than without it.)

# Experimental Designs

- To apply Scaled Average BE, at least the Reference product must be replicated. The classic two-period TR, RT design cannot be used
- Three-Period Crossover Design

period		
1	2	3
T	R	R
R	T	R
R	R	T

# Experimental Designs (cont'd.)

- Four-Period Crossover Design

period			
1	2	3	4
T	R	T	R
R	T	R	T

# Experimental Designs (cont'd.)

- Because both products are replicated in the four-period design, it is possible to make a statistical comparison of  $\sigma_{WT}$  and  $\sigma_{WR}$ . For this reason, attention was concentrated on this design.

There have been attempts to compare within-subject variances within the classic TR, RT two-period design (see, e.g., Guilbaud, 1993 *J. Amer. Stat. Assoc.*), but such a comparison may be confounded with other factors, and would not be expected to be as efficient as that available with the four-period fully replicated design.



## Regular Unscaled Average BE with Narrower Limits

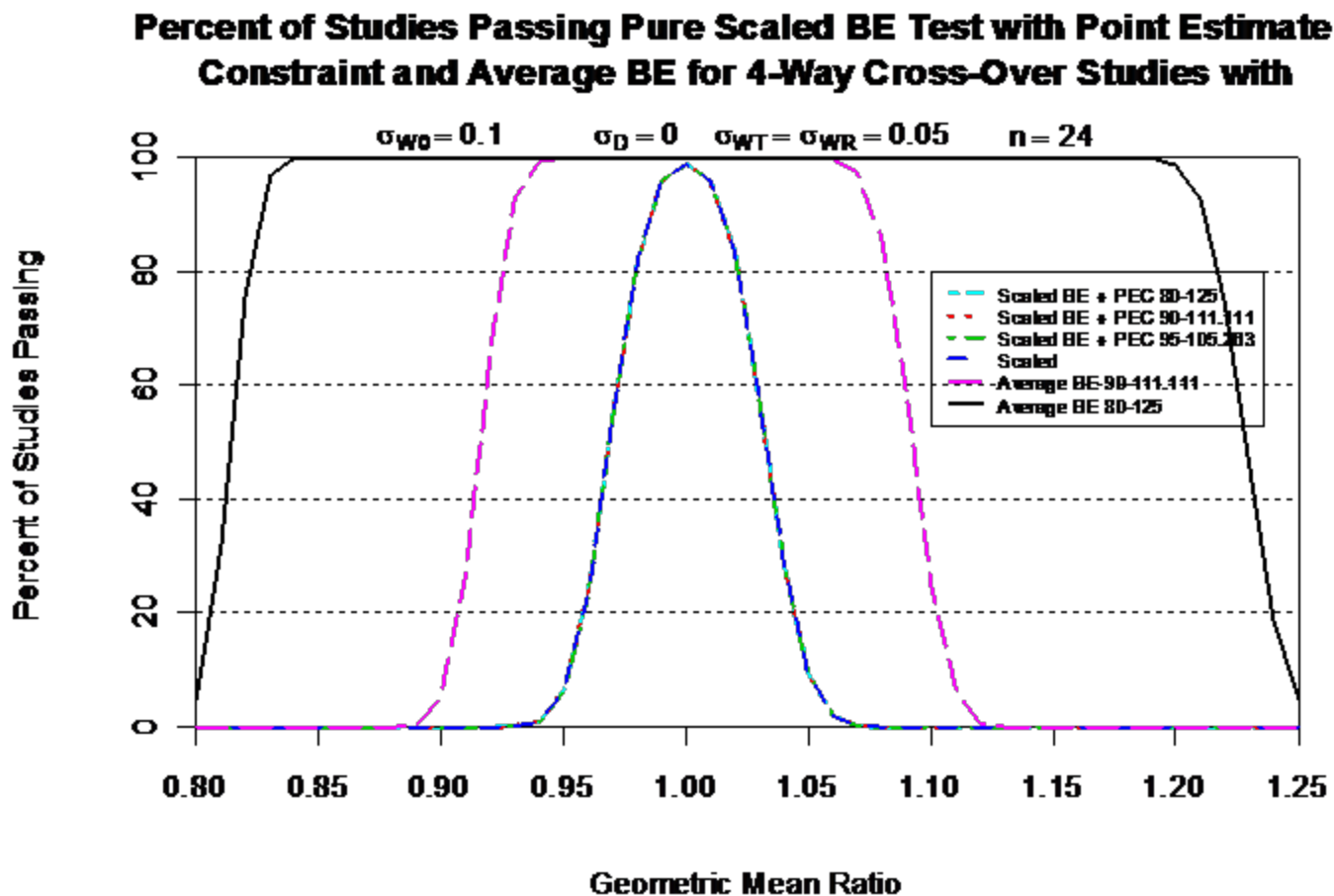
- The Working Group also looked at regular average BE with BE limits of 90-111.11%.
- This approach could be implemented with the classic TR, RT crossover design. However, use of that design, as already discussed, would not permit efficient comparison of within-subject variances.

## Regular Unscaled Average BE with Narrower Limits (cont'd.)

- One of the arguments for scaled average BE is that the level of variability may be indicative of the therapeutic ratio – if a drug is highly variable, it presumably has a wide therapeutic window. Conversely, if a drug shows low variability, the therapeutic window might be narrow.

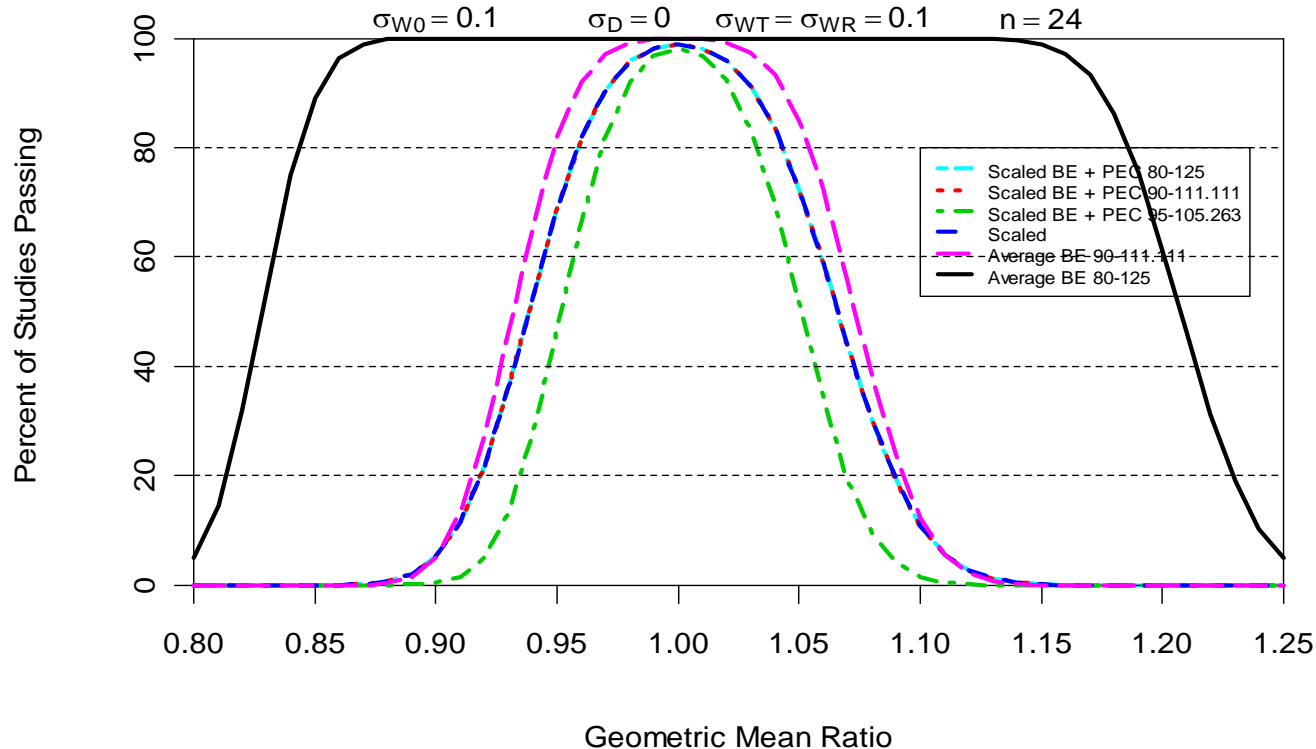
Use of regular average BE with narrower limits takes no direct account of the amount of variability.

## Results for Case 3: $\sigma_{WT} = \sigma_{WR}$ , $n=24$



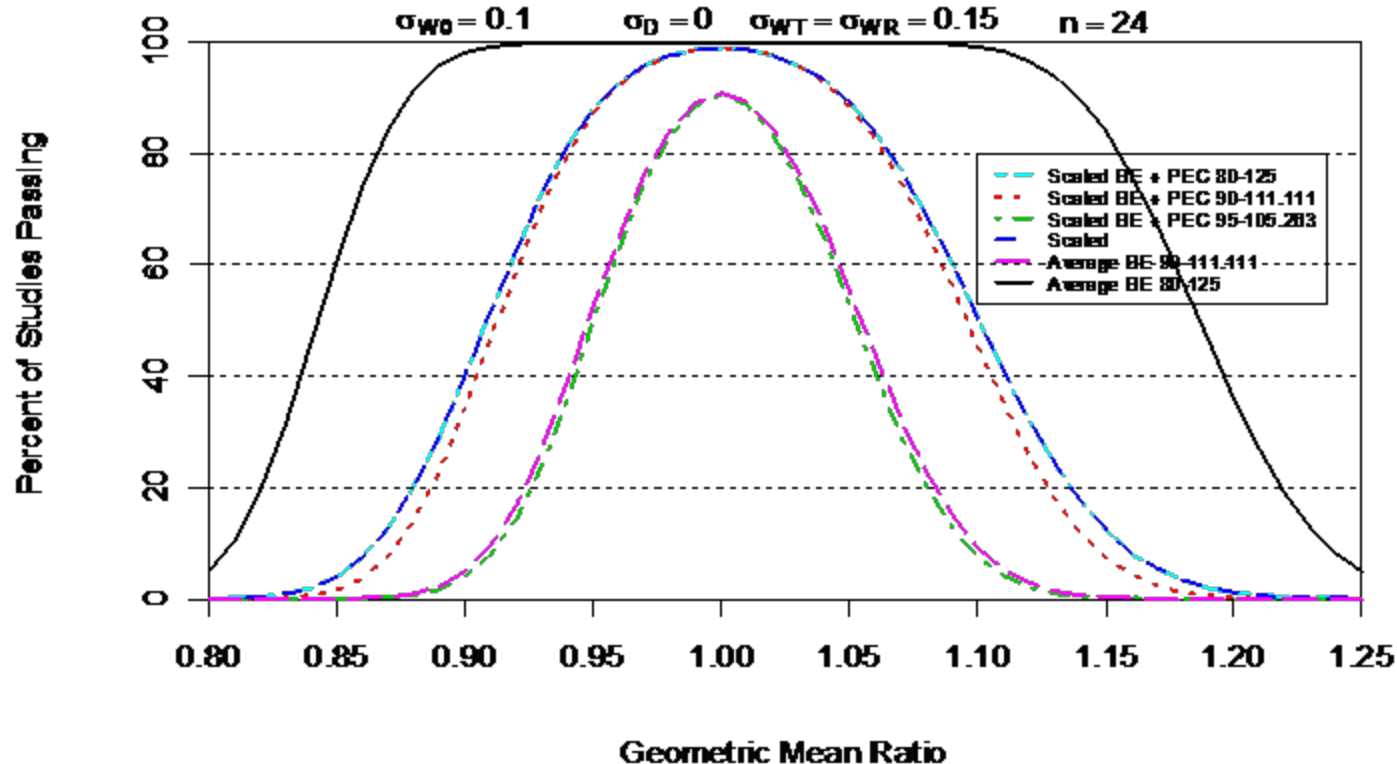
# Results for Case 3: $\sigma_{WT} = \sigma_{WR}$ , $n=24$ (cont'd.)

**Percent of Studies Passing Pure Scaled BE Test with Point Estimate Constraint and Average BE for 4-Way Cross-Over Studies with**

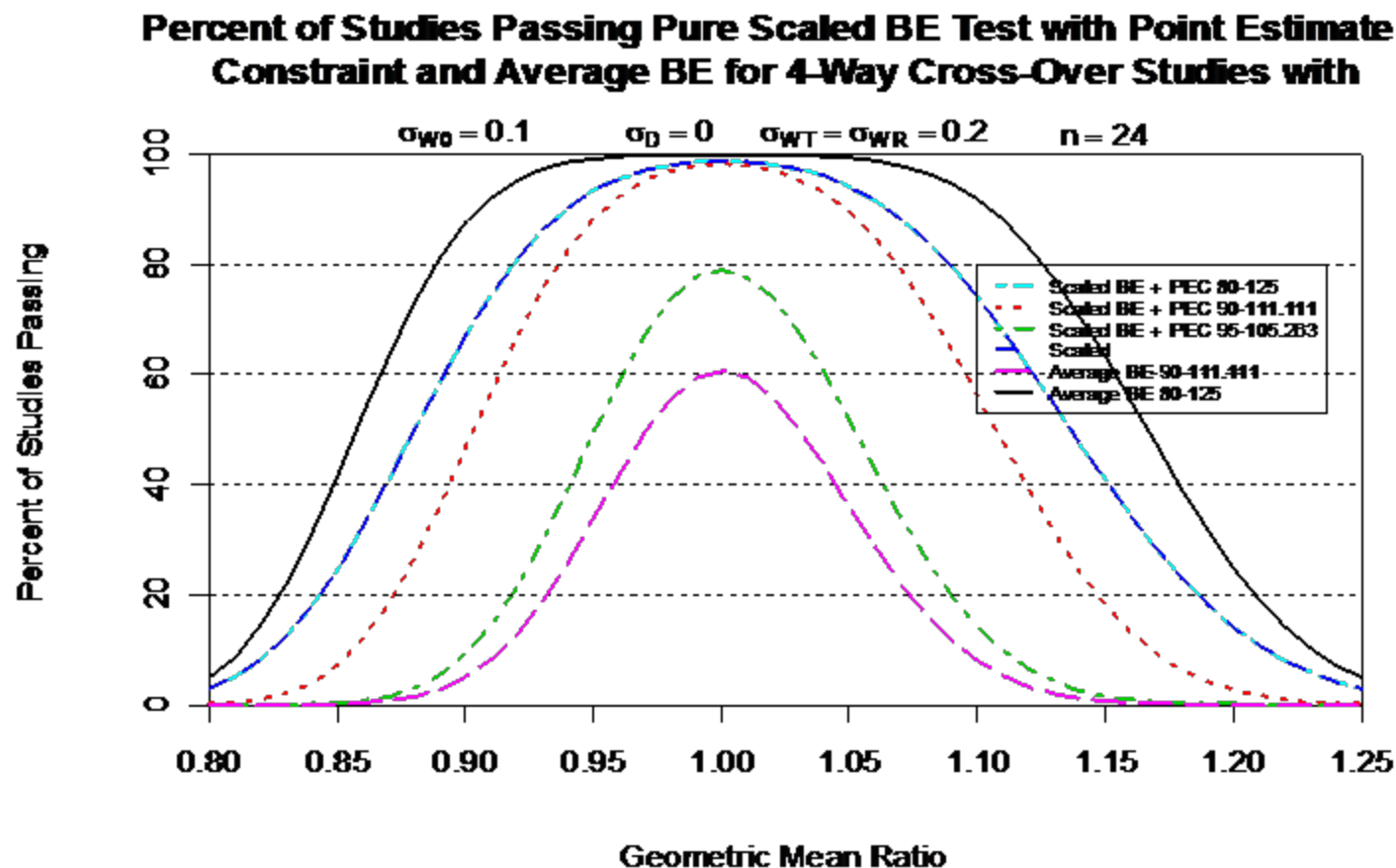


# Results for Case 3: $\sigma_{WT} = \sigma_{WR}$ , $n=24$ (cont'd.)

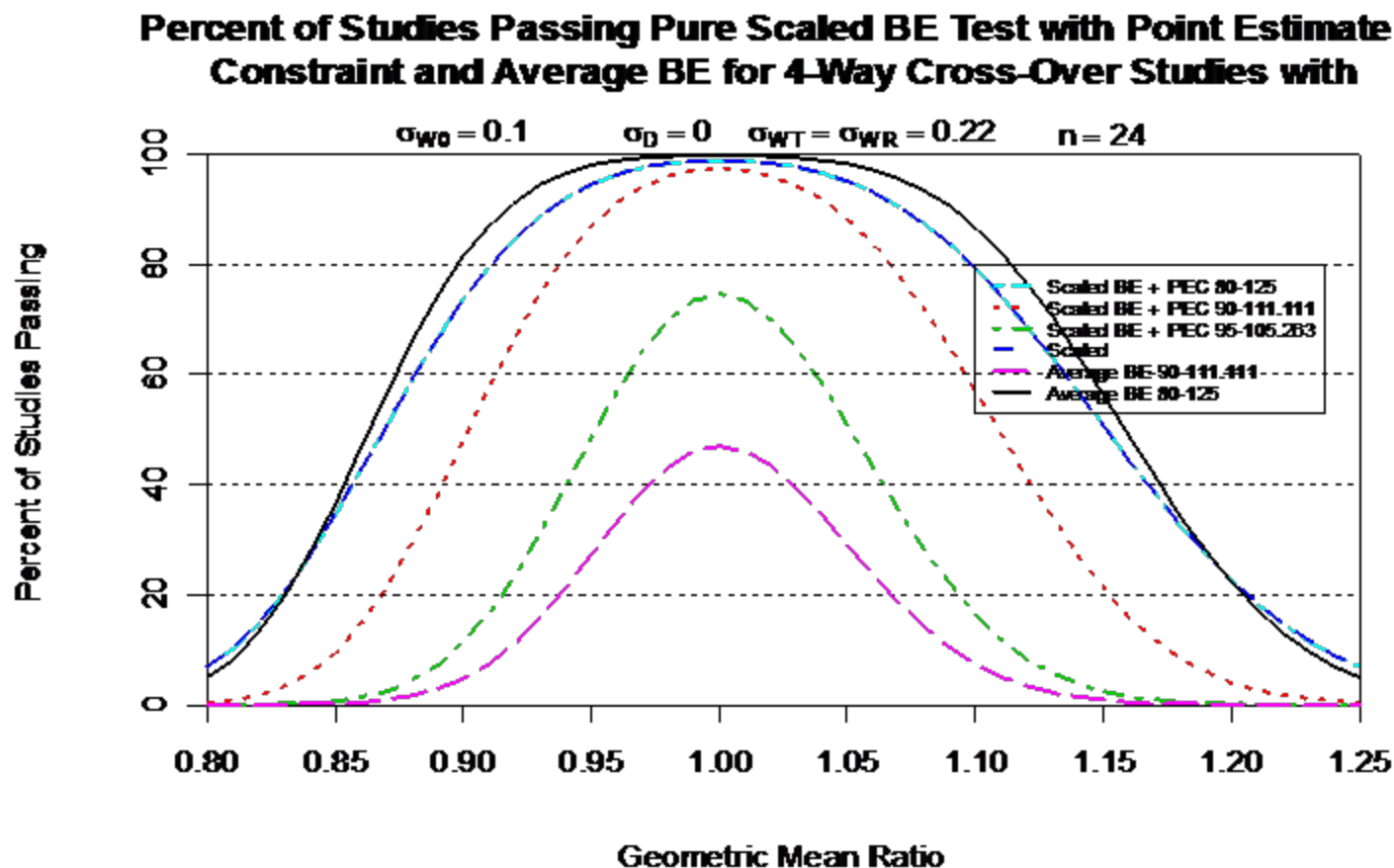
**Percent of Studies Passing Pure Scaled BE Test with Point Estimate Constraint and Average BE for 4-Way Cross-Over Studies with**



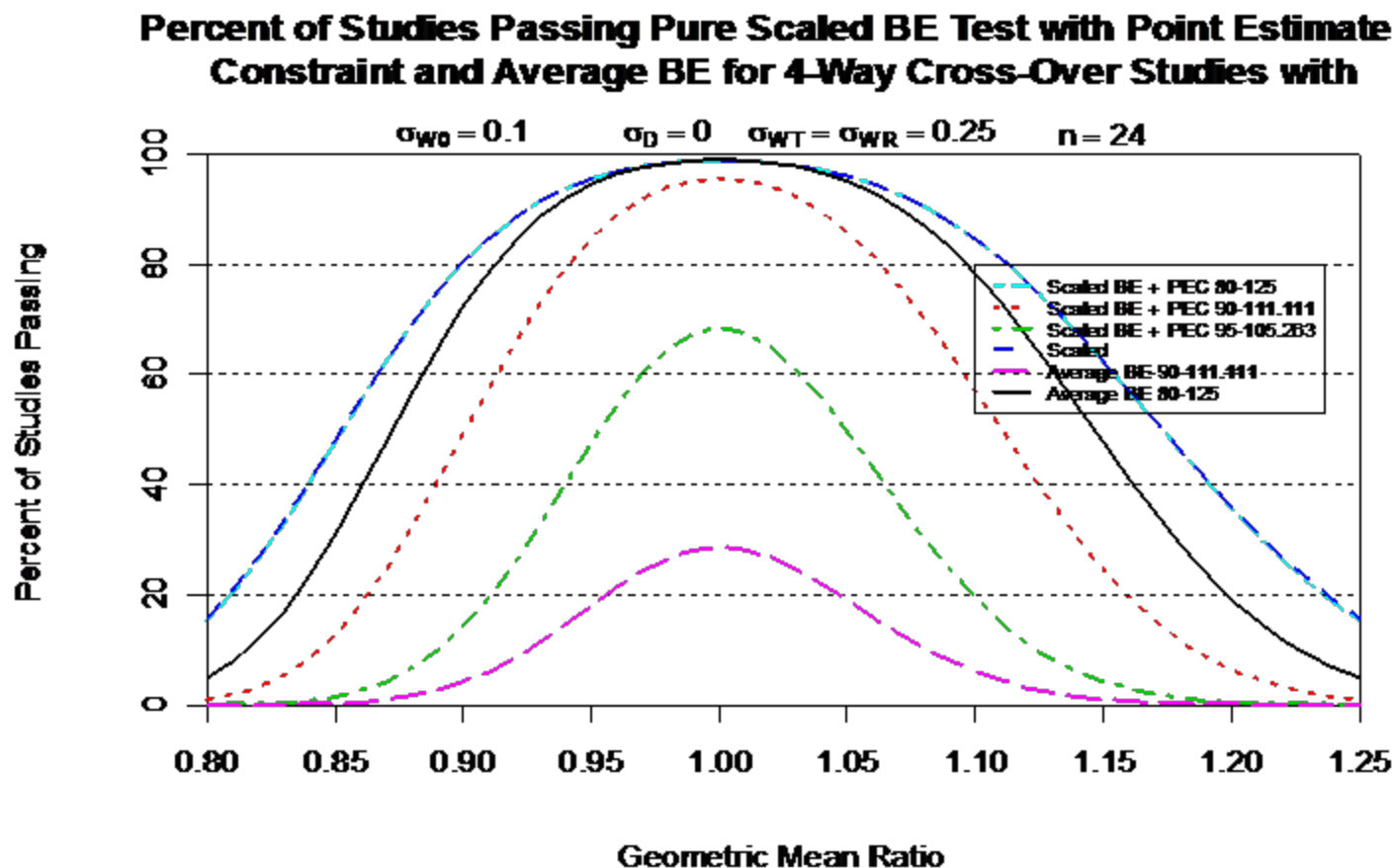
## Results for Case 3: $\sigma_{WT} = \sigma_{WR}$ , $n=24$ (cont'd.)



## Results for Case 3: $\sigma_{WT} = \sigma_{WR}$ , $n=24$ (cont'd.)

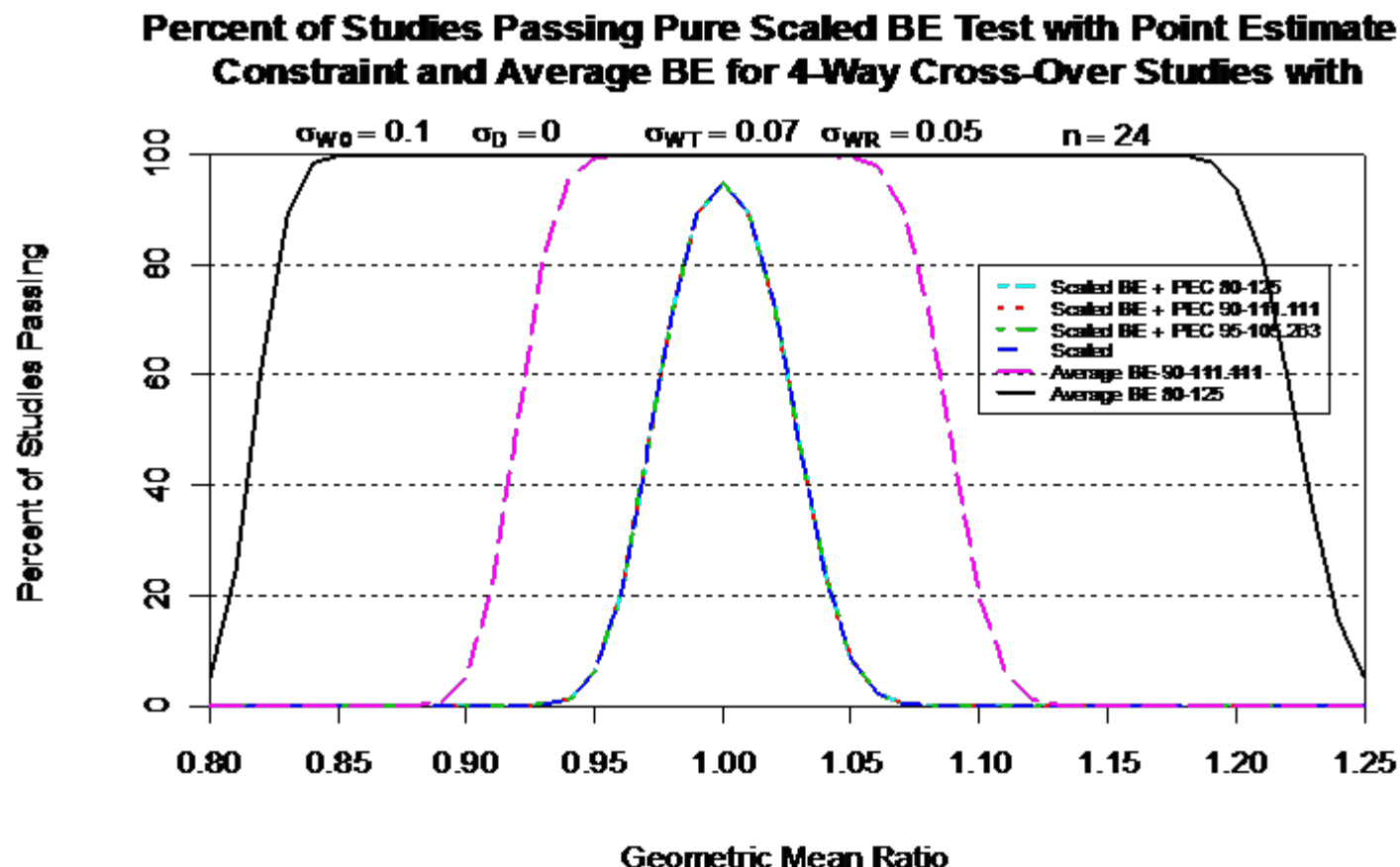


## Results for Case 3: $\sigma_{WT} = \sigma_{WR}$ , $n=24$ (cont'd.)

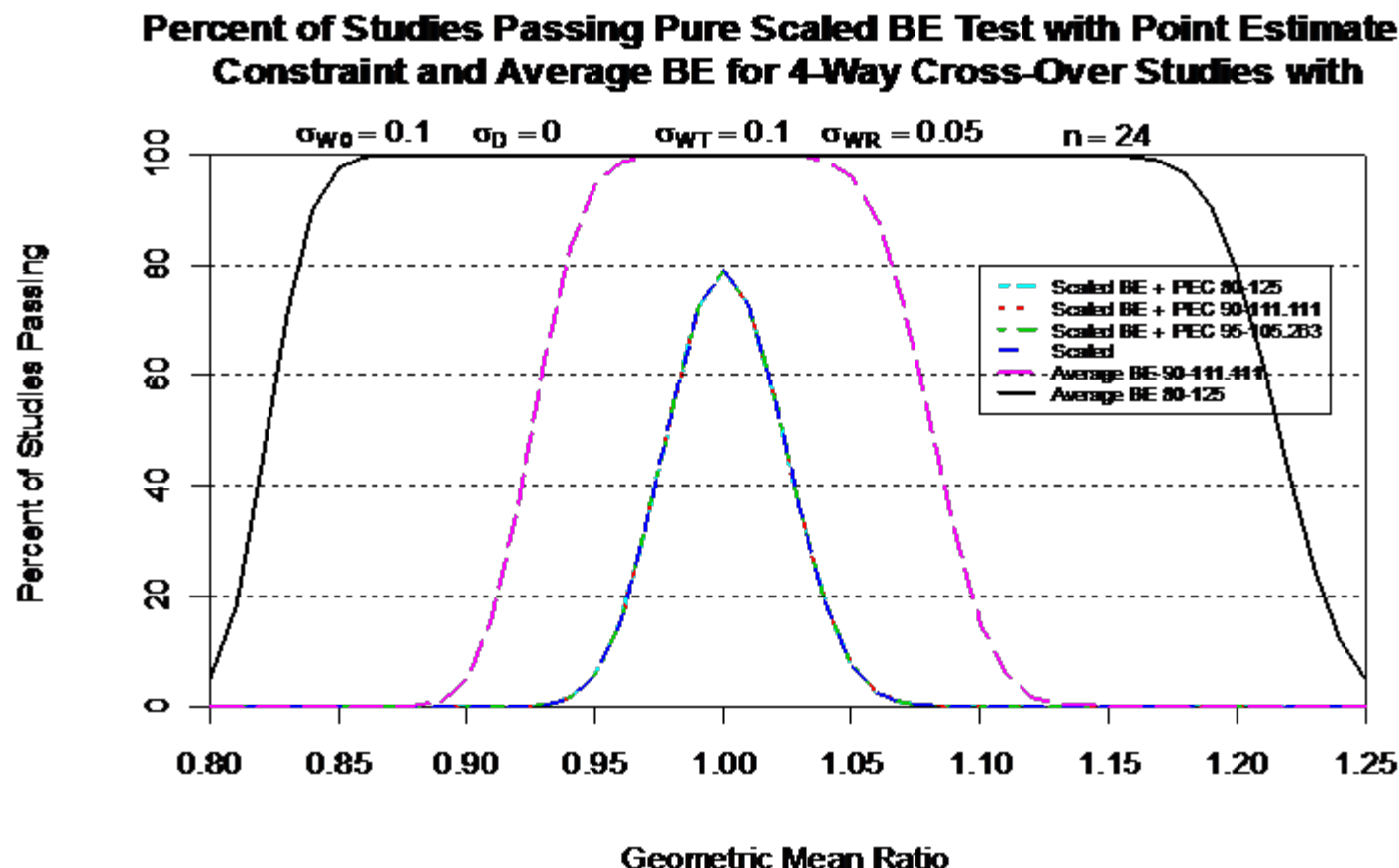




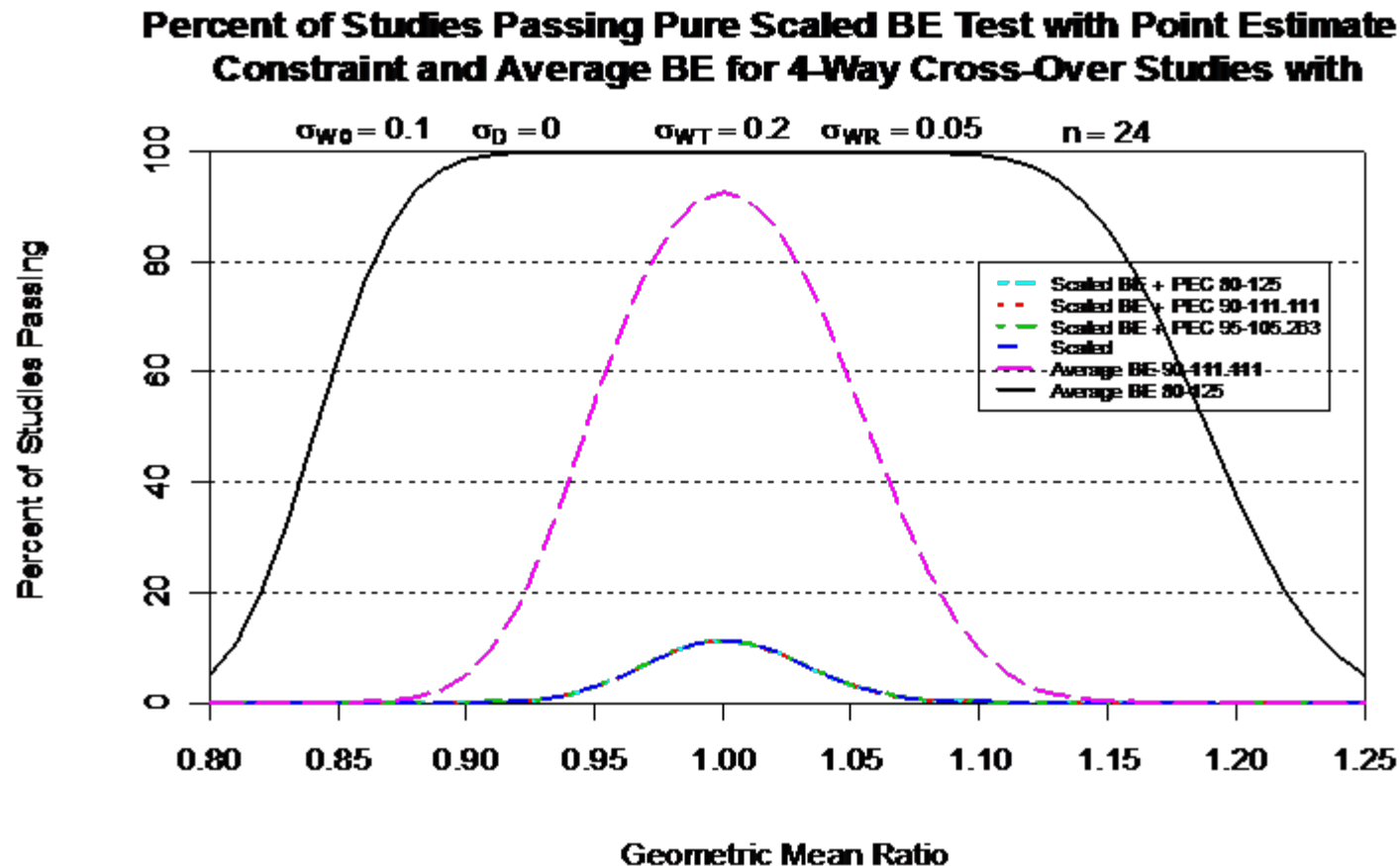
# Results for Case 3: $\sigma_{WT} > \sigma_{WR}$ , $n=24$ (cont'd.)



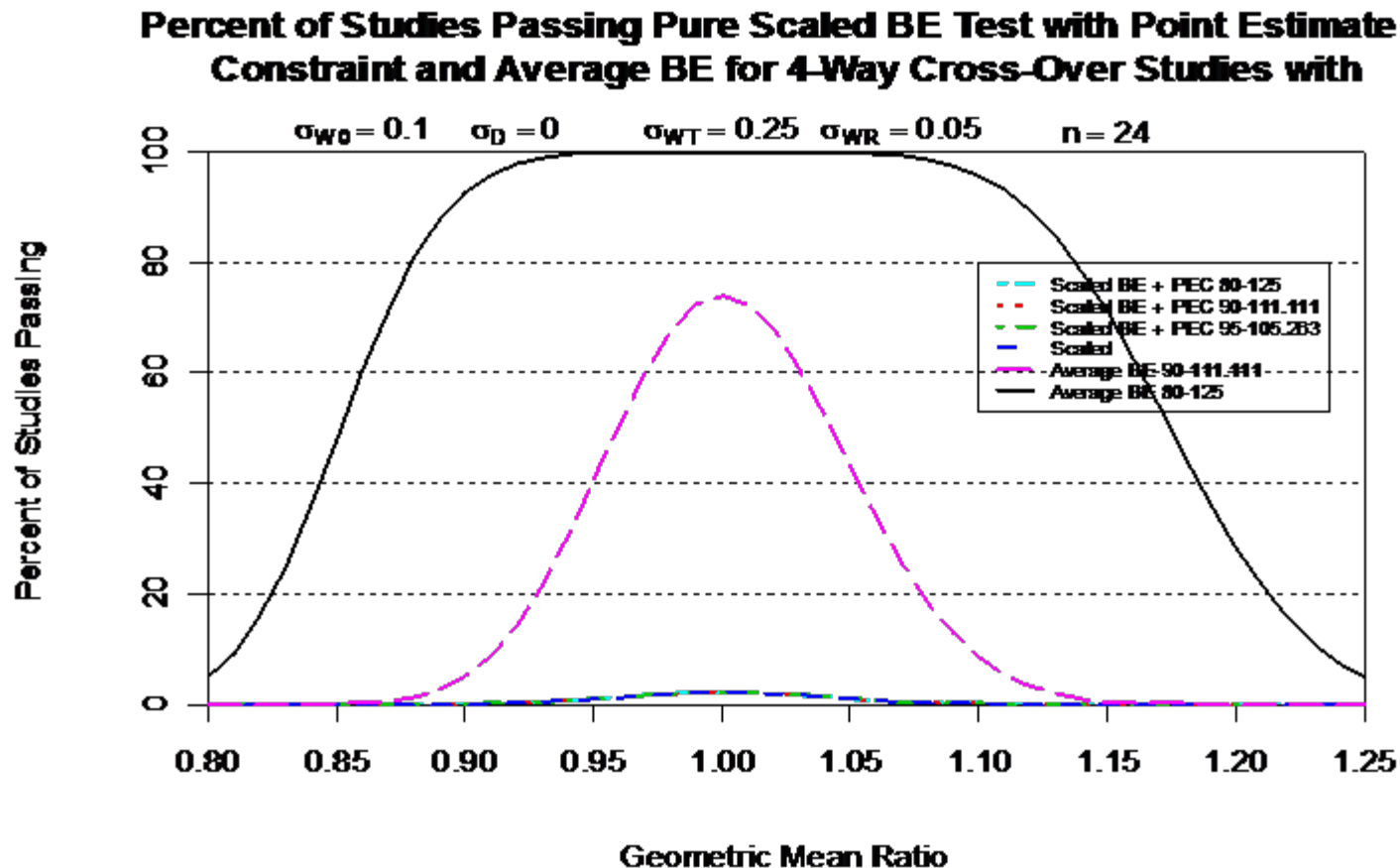
## Results for Case 3: $\sigma_{WT} > \sigma_{WR}$ , $n=24$ (cont'd.)



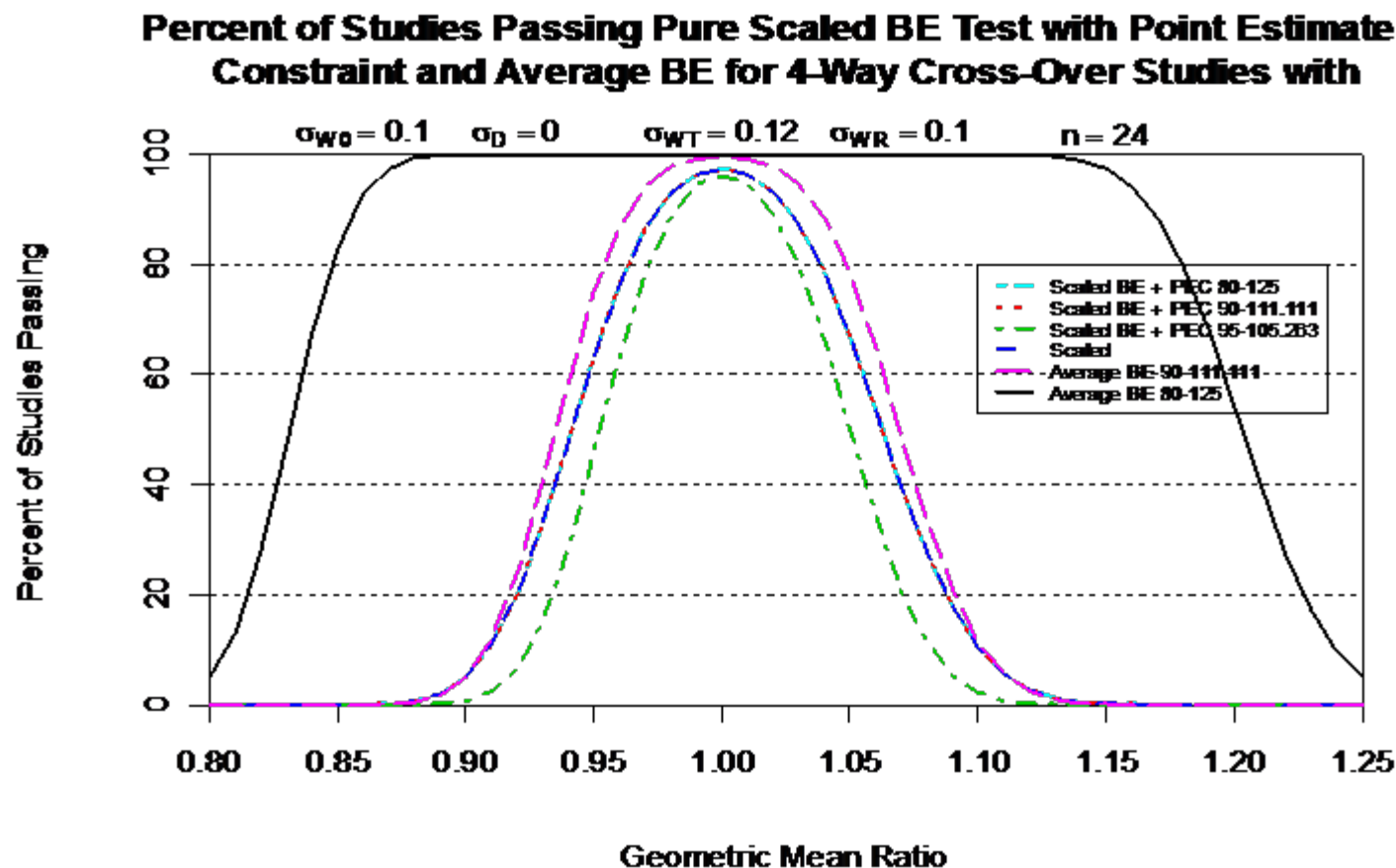
# Results for Case 3: $\sigma_{WT} > \sigma_{WR}$ , $n=24$ (cont'd.)



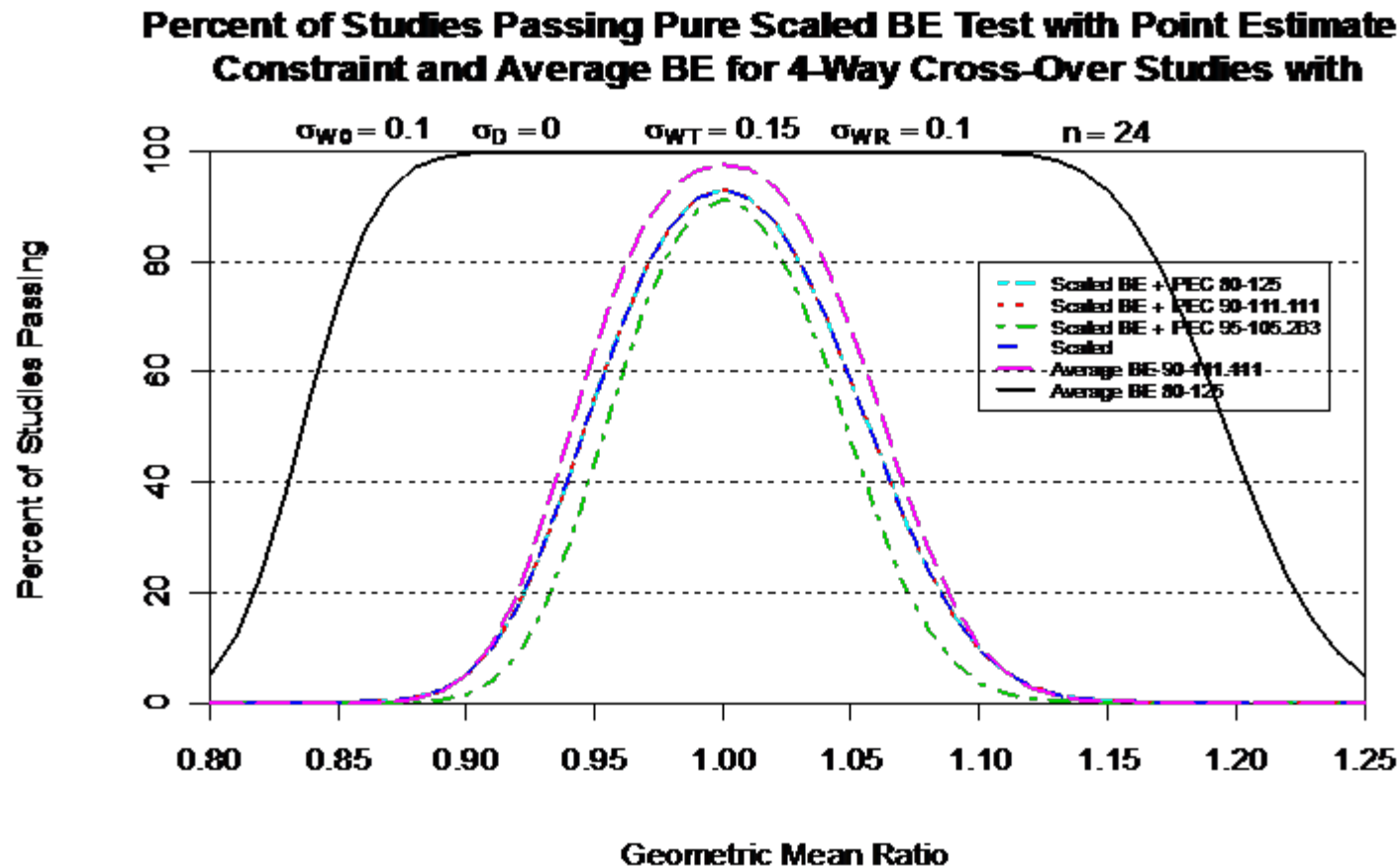
# Results for Case 3: $\sigma_{WT} > \sigma_{WR}$ , $n=24$ (cont'd.)



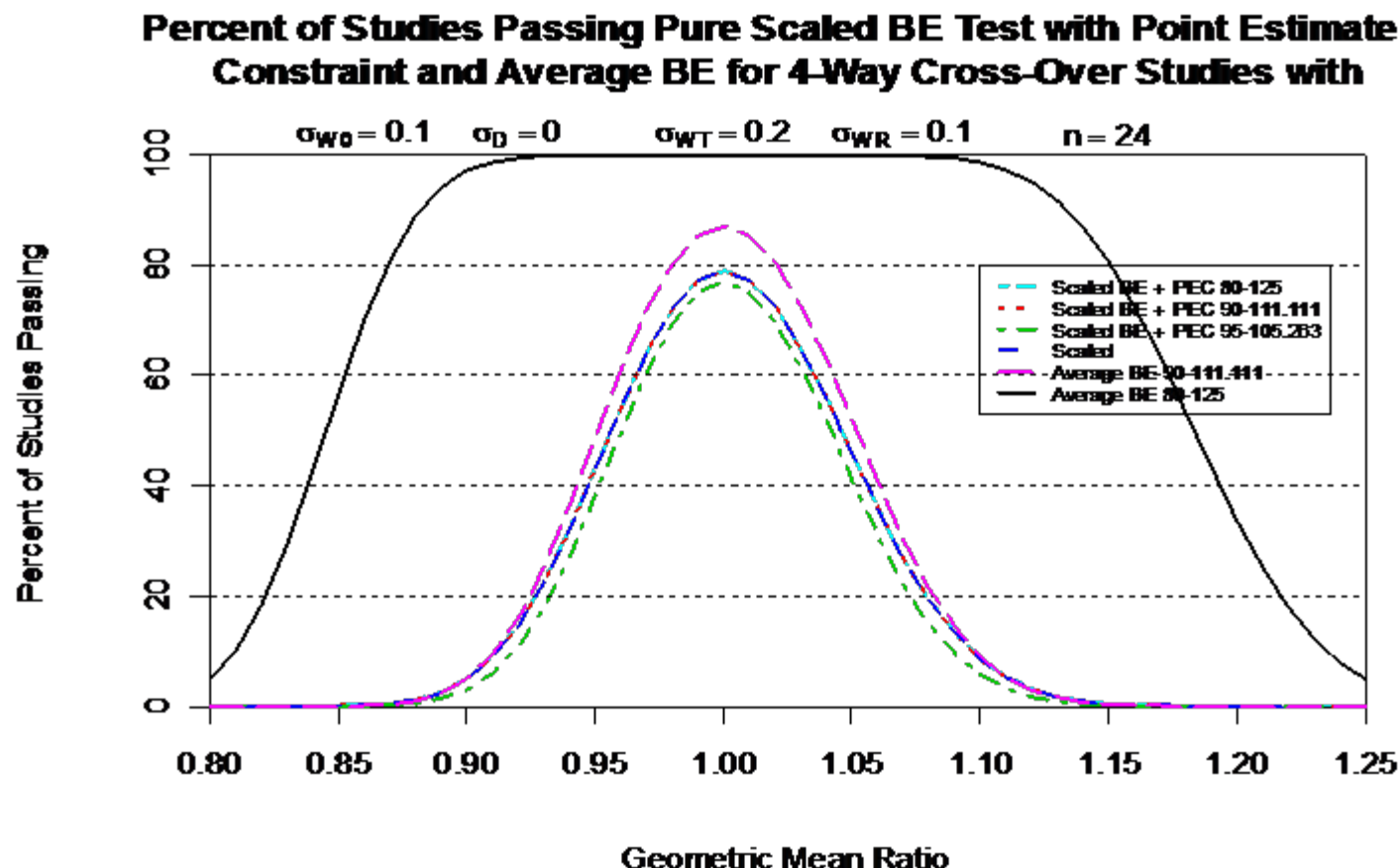
## Results for Case 3: $\sigma_{WT} > \sigma_{WR}$ , $n=24$ (cont'd.)



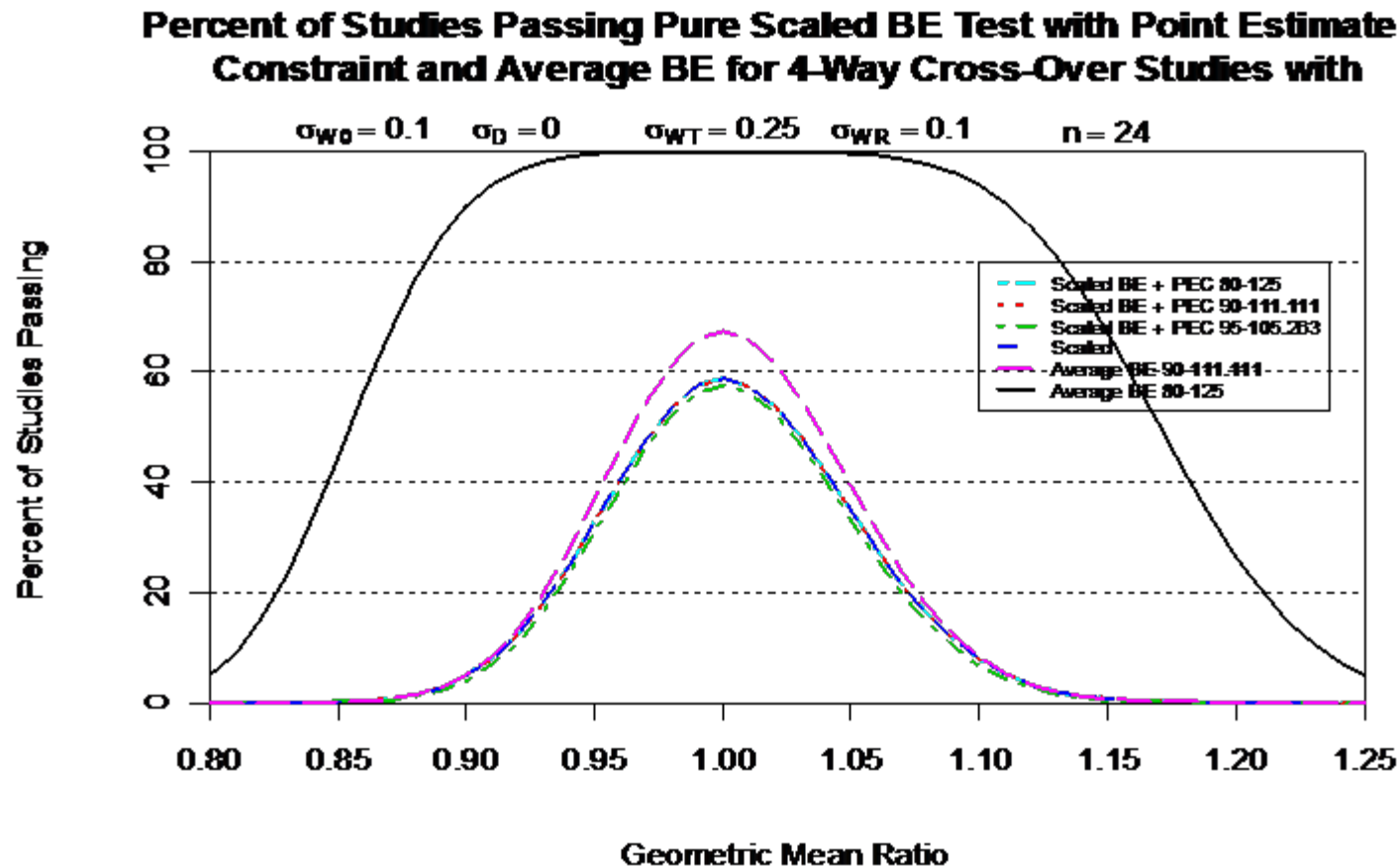
# Results for Case 3: $\sigma_{WT} > \sigma_{WR}$ , $n=24$ (cont'd.)



## Results for Case 3: $\sigma_{WT} > \sigma_{WR}$ , $n=24$ (cont'd.)

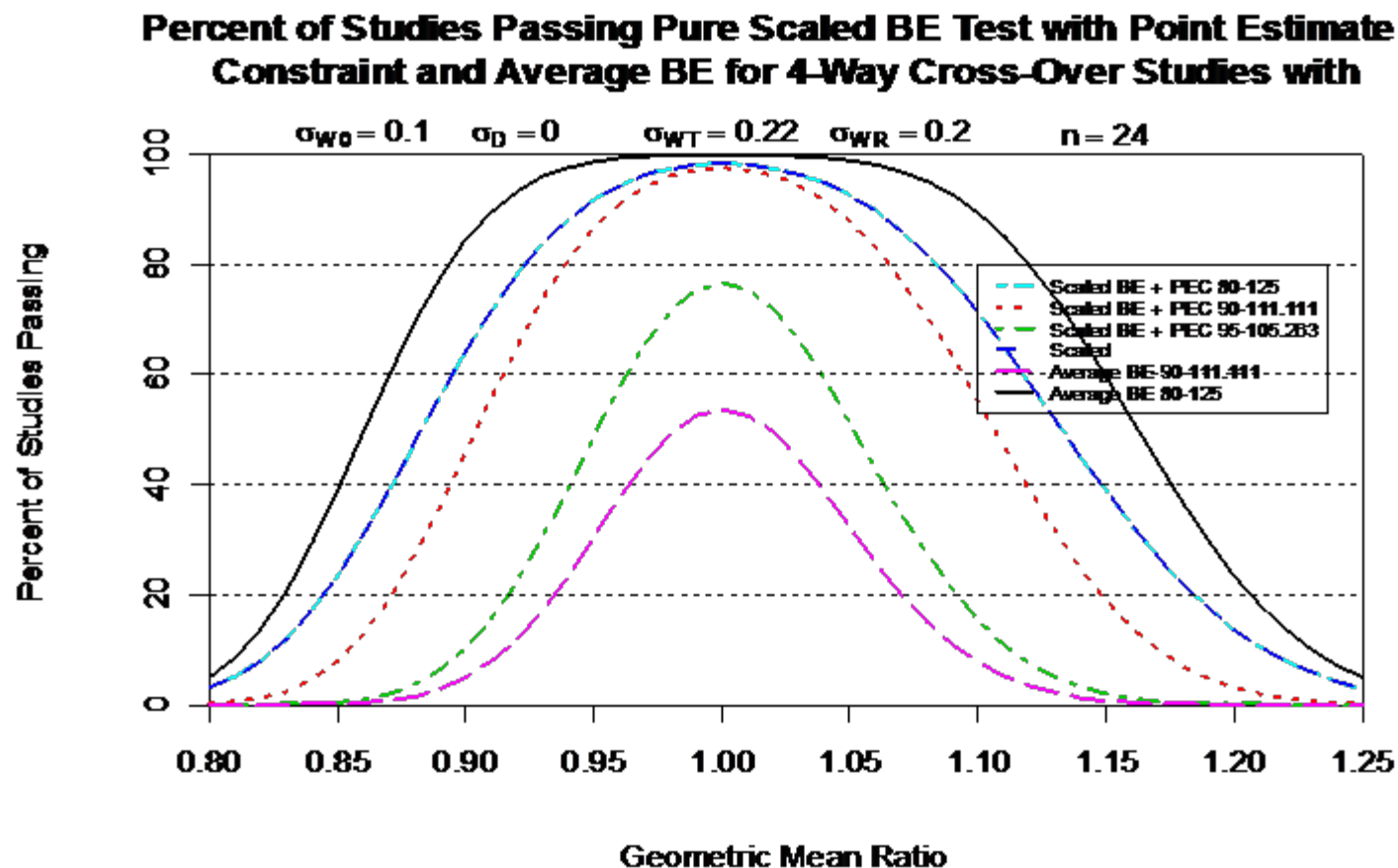


# Results for Case 3: $\sigma_{WT} > \sigma_{WR}$ , $n=24$ (cont'd.)

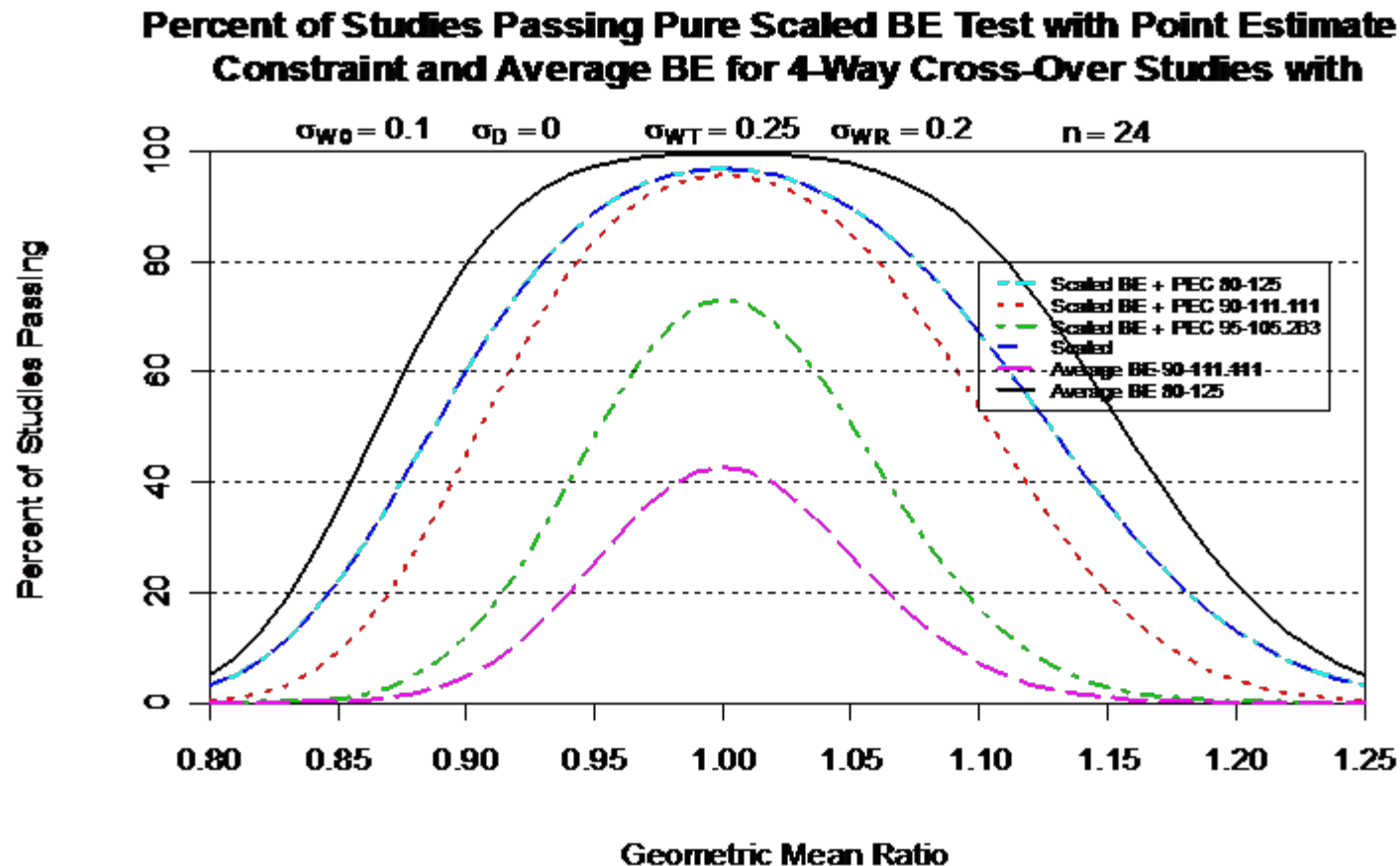




## Results for Case 3: $\sigma_{WT} > \sigma_{WR}$ , $n=24$ (cont'd.)

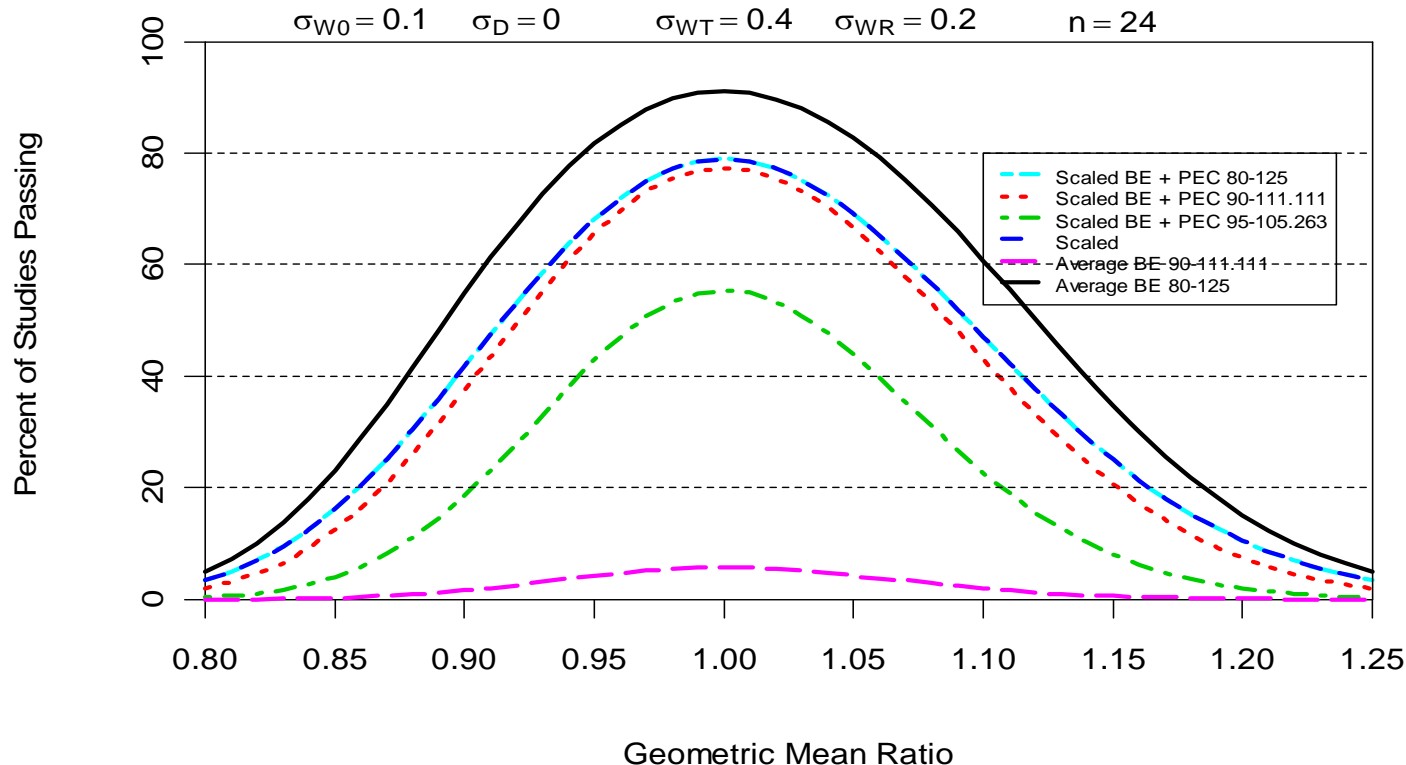


# Results for Case 3: $\sigma_{WT} > \sigma_{WR}$ , $n=24$ (cont'd.)



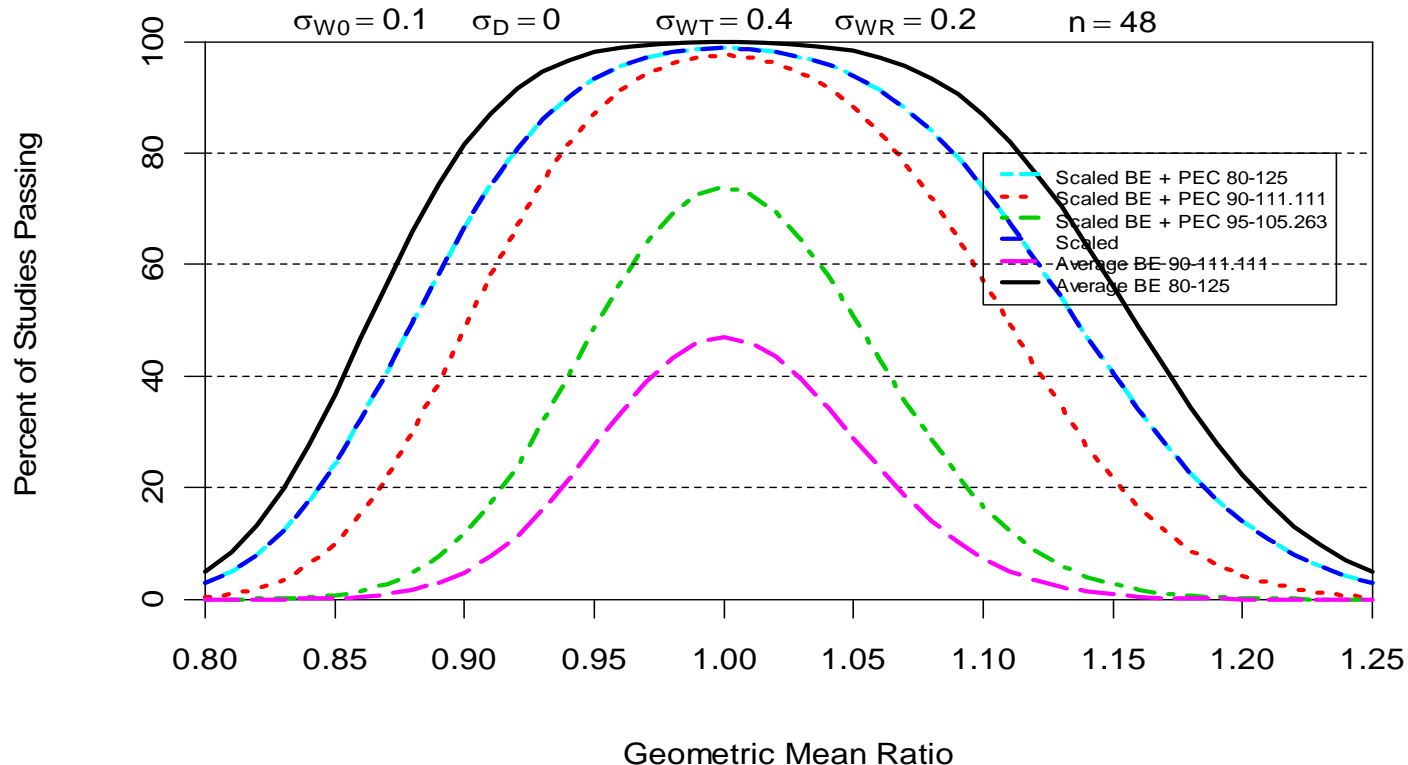
## Results for Case 3: $\sigma_{WT} > \sigma_{WR}$ , $n=24$ (cont'd.)

**Percent of Studies Passing Pure Scaled BE Test with Point Estimate Constraint and Average BE for 4-Way Cross-Over Studies with**



## Results for Case 3: $\sigma_{WT} > \sigma_{WR}$ , $n=48$

Percent of Studies Passing Pure Scaled BE Test with Point Estimate Constraint and Average BE for 4-Way Cross-Over Studies with

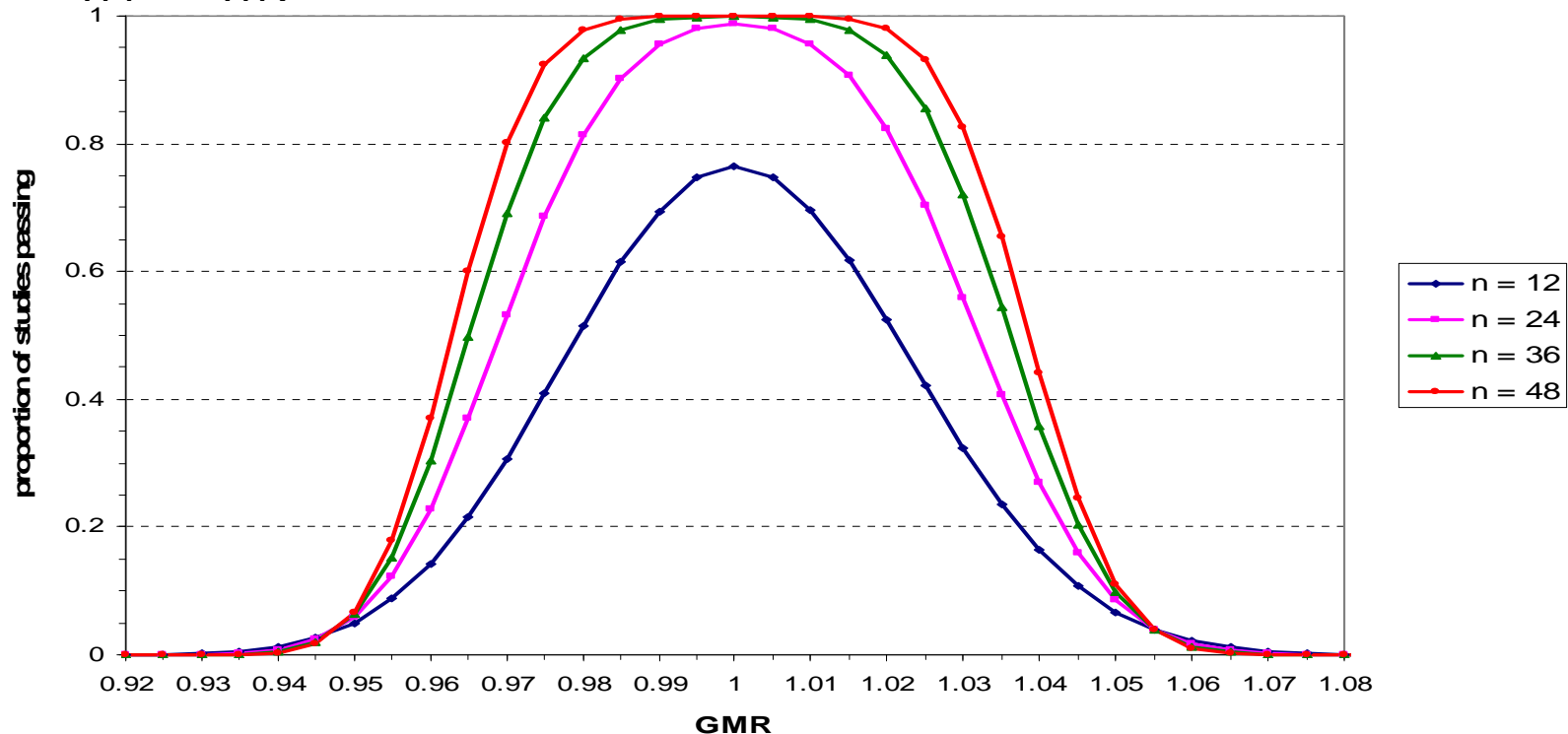


## **Requiring the 90% Confidence Interval to Contain 1.0: Problematic**

- Another proposal that has been considered is to require the usual 90% confidence interval for the GMR to contain the value 1.0.
- While I (DJS) understand the surface appeal of this requirement, it can have unintended consequences

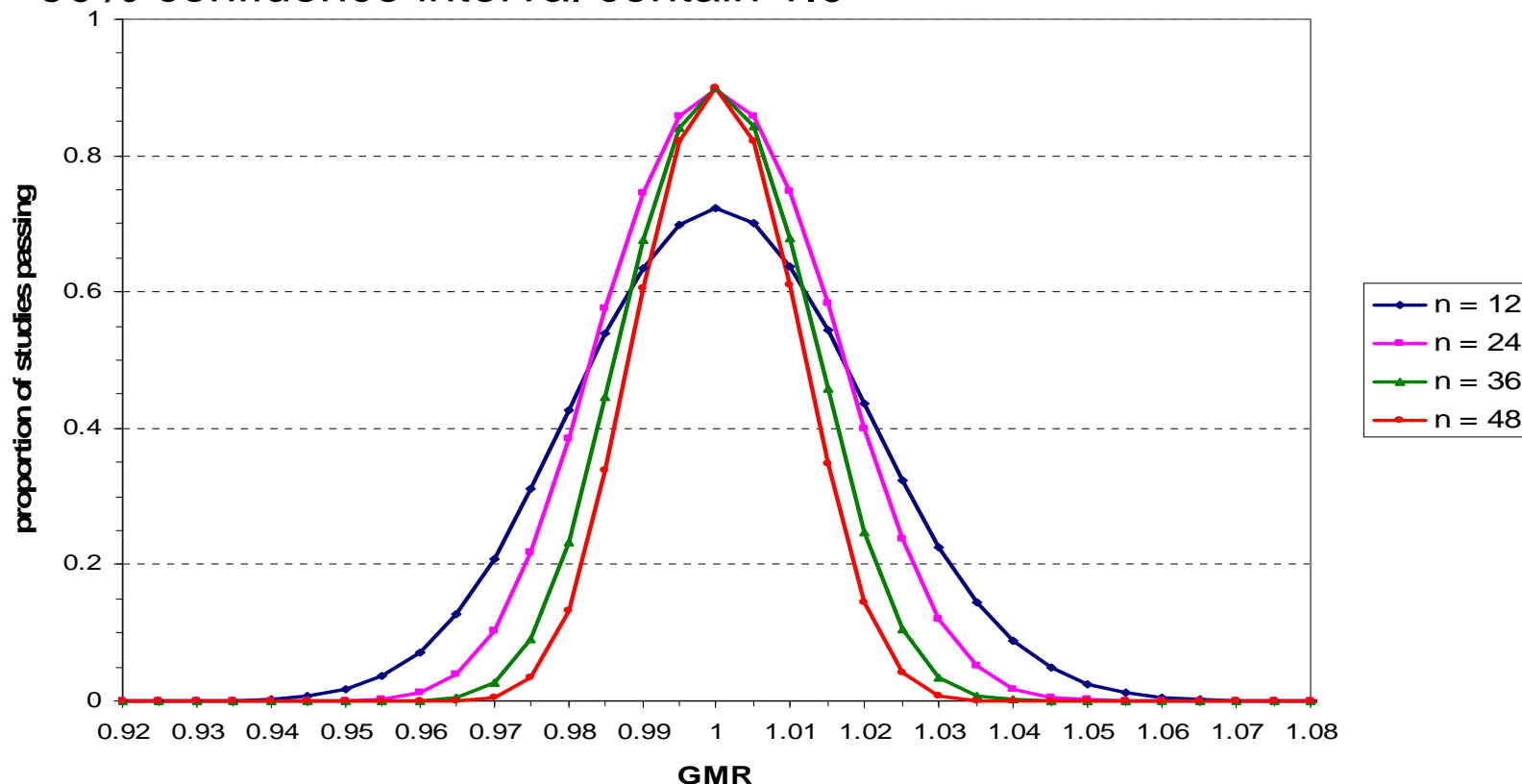
# Requiring the 90% Confidence Interval to Contain 1.0: Problematic (cont'd.)

- Here is an example of Scaled Average BE (Case 3,  $\sigma_{WT}=\sigma_{WR}=0.05$ ) for four different sample sizes



# Requiring the 90% Confidence Interval to Contain 1.0: Problematic (cont'd.)

- Here is the same case, but with the added requirement that the 90% confidence interval contain 1.0



## Requiring the 90% Confidence Interval to Contain 1.0: Problematic (cont'd.)

- In this example, even for GMR very close to 1.0 (e.g. 0.98 – closer than required by potency testing), the higher the sample size, the **lower** the chance of passing the test. Generic product sponsors would have a *disincentive* to study more subjects.
- Also, even if the  $GMR = 1.0$ , no matter how great the sample size the chance of passing never exceeds 0.90, since there is always that 10% chance that the 90% confidence interval will not contain the true value of 1.0.
- In my (DJS) personal opinion, this requirement is a bad idea.

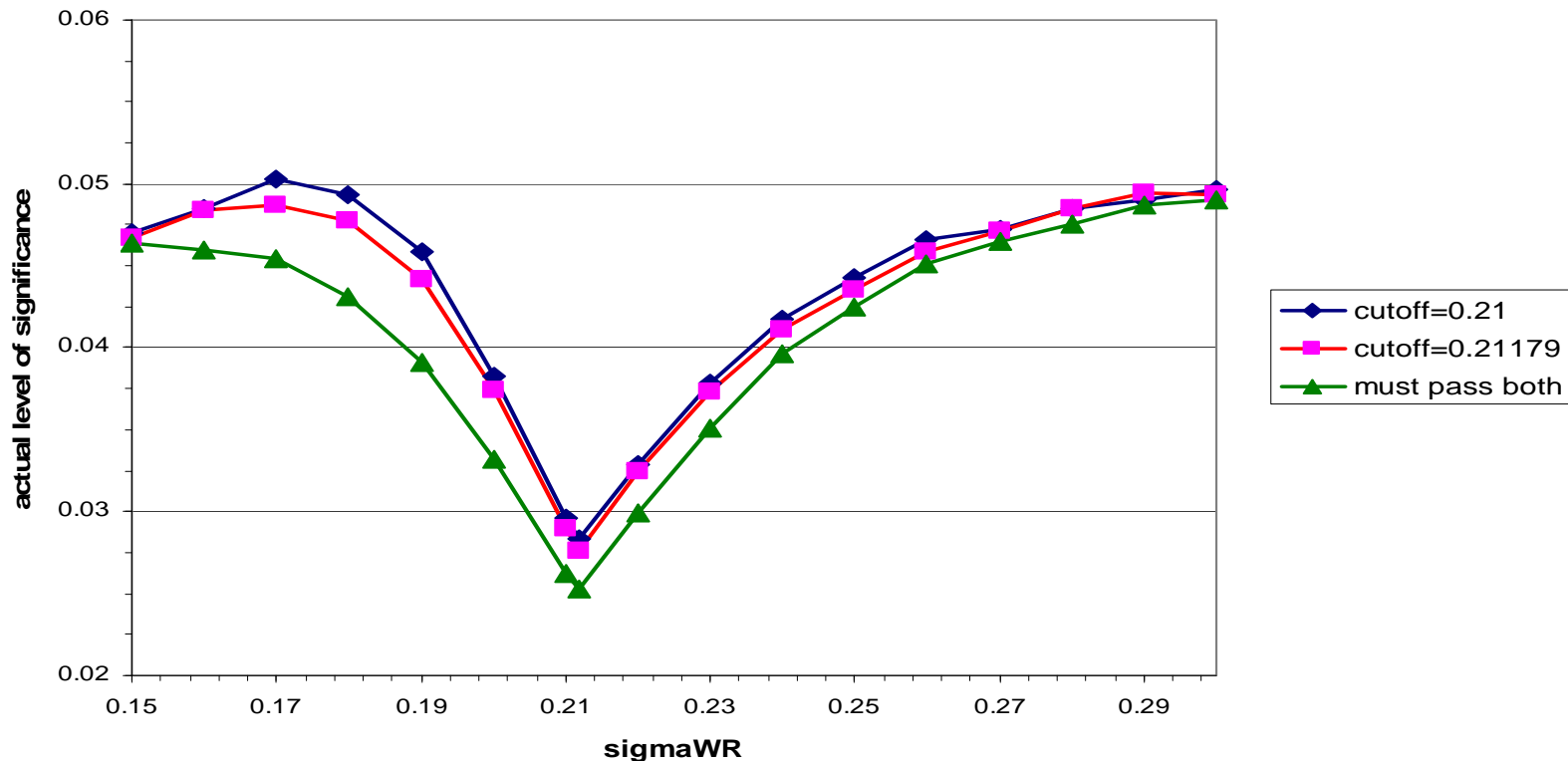


## Ensuring that the BE Limits are Never Wider than 80-125%

- One concern with Scaled Average BE is that the estimate of  $\sigma_{WR}$  from a particular study might be high, and we would be using BE limits wider than 80-125%.
- There are two ways to prevent this.
  - Establish a cutoff value on  $s_{WR}$ , the *estimate* of  $\sigma_{WR}$ , and switch to regular unscaled BE with limits of 80-125% for studies where  $s_{WR}$  exceeds the cutoff. For Case 3, a reasonable cutoff would be  $s_{WR} = 0.21179$ , or possibly 0.21.
  - Use “Must Pass Both” – require every study to pass the criteria we propose (e.g. scaled average BE, possibly with a PEC) and *also* pass regular unscaled BE with limits of 80-125%.

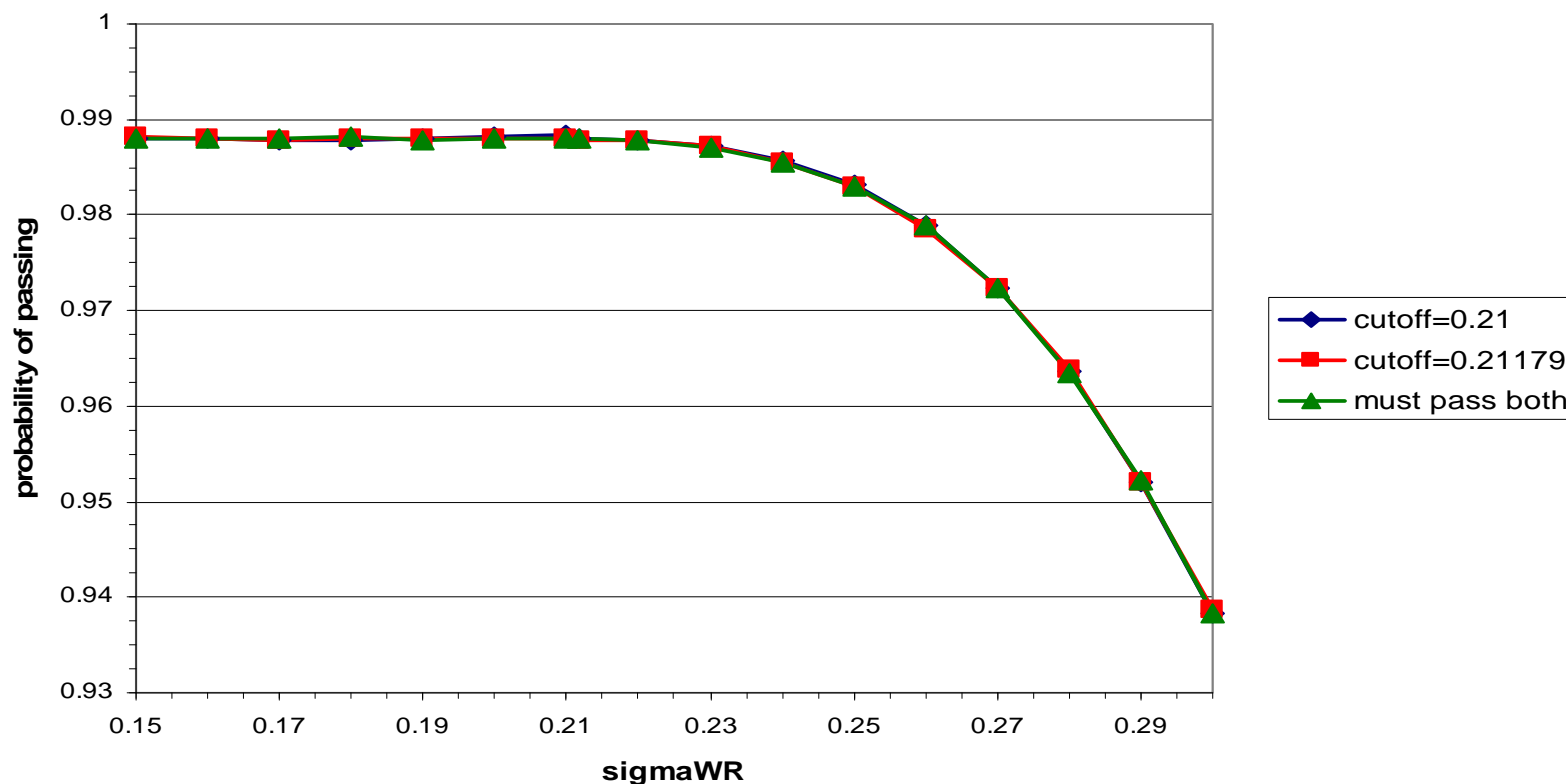
# Ensuring that the BE Limits are Never Wider than 80-125%

- Both of these methods preserve the actual level of significance at no more than 5%



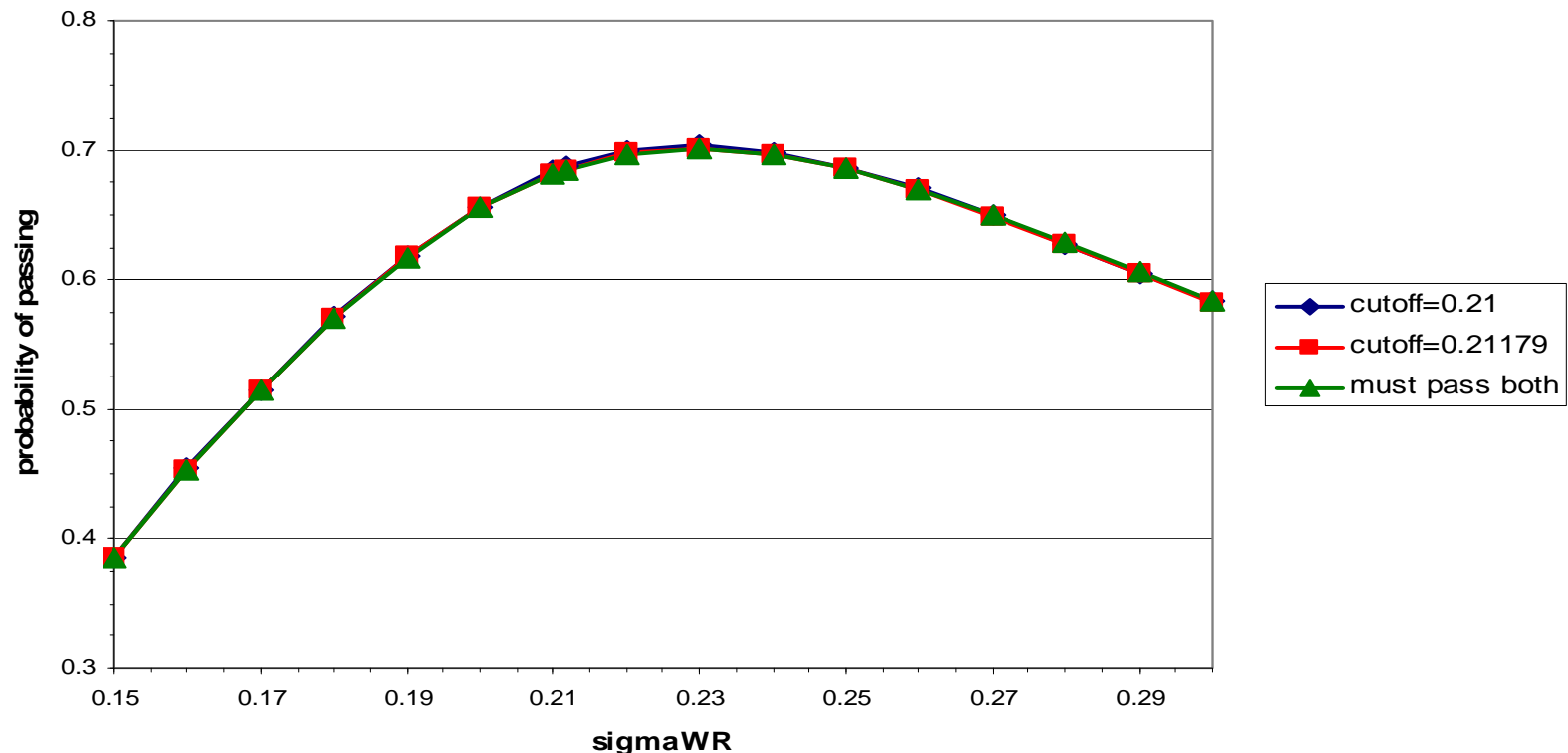
# Ensuring that the BE Limits are Never Wider than 80-125%

- When  $GMR = 1.0$ , there is almost no difference in power for the two approaches



# Ensuring that the BE Limits are Never Wider than 80-125%

- When  $GMR = 0.90$ , there is also almost no difference in power for the two approaches



# Pharmaceutical Quality of Narrow Therapeutic Index (NTI) Drug Products

*Advisory Committee for Pharmaceutical Science  
and  
Clinical Pharmacology  
July 26, 2011*

**Wenlei Jiang, Ph.D.**  
**Office of Generic Drugs**

# Background

- At the conclusion of the April 2010 ACPS meeting on NTI drugs, the committee voted 11-2 that the current bioequivalence standards are not sufficient for NTI drugs. The Committee commented:
  - Replicate studies are important
  - The Agency should look at manufacturing data on excipients from existing formularies
  - The requirements for confidence intervals should perhaps be narrower (90-111%) and should include 100% (or 1.0)

# Objectives

- Evaluate pharmaceutical quality of approved NTI drug products
- Assess whether some pharmaceutical quality standards should be strengthened for NTI drug products

# NTI Pharmaceutical Quality Survey

- NTI product formulation design and manufacturing process
- NTI product specification tests, analytical methods and acceptance criteria (e.g. potency, dissolution, impurity)
- NTI product batch release and stability data
- Drug product recall data submitted to FDA (Jan 1<sup>st</sup>, 2000 - May 3<sup>rd</sup>, 2011)



# Selected Oral NTI Products for Survey

Drug Name	Currently Available Oral Dosage Forms	Earliest Year Approved
Carbamazepine	Tablet, Chewable tablet, Extended Release (ER) tablet, ER capsule, Suspension	1968
Digoxin	Elixir, Tablet	1997
Levothyroxine	Tablet, Capsule	2000
Phenytoin	ER capsule, Chewable tablet, Suspension	1976
Theophylline	Solution, ER tablet, Sustained release (SR) capsule	1990
Warfarin	Tablet	1954
Lithium	Tablet, Capsule, ER Tablet	1970

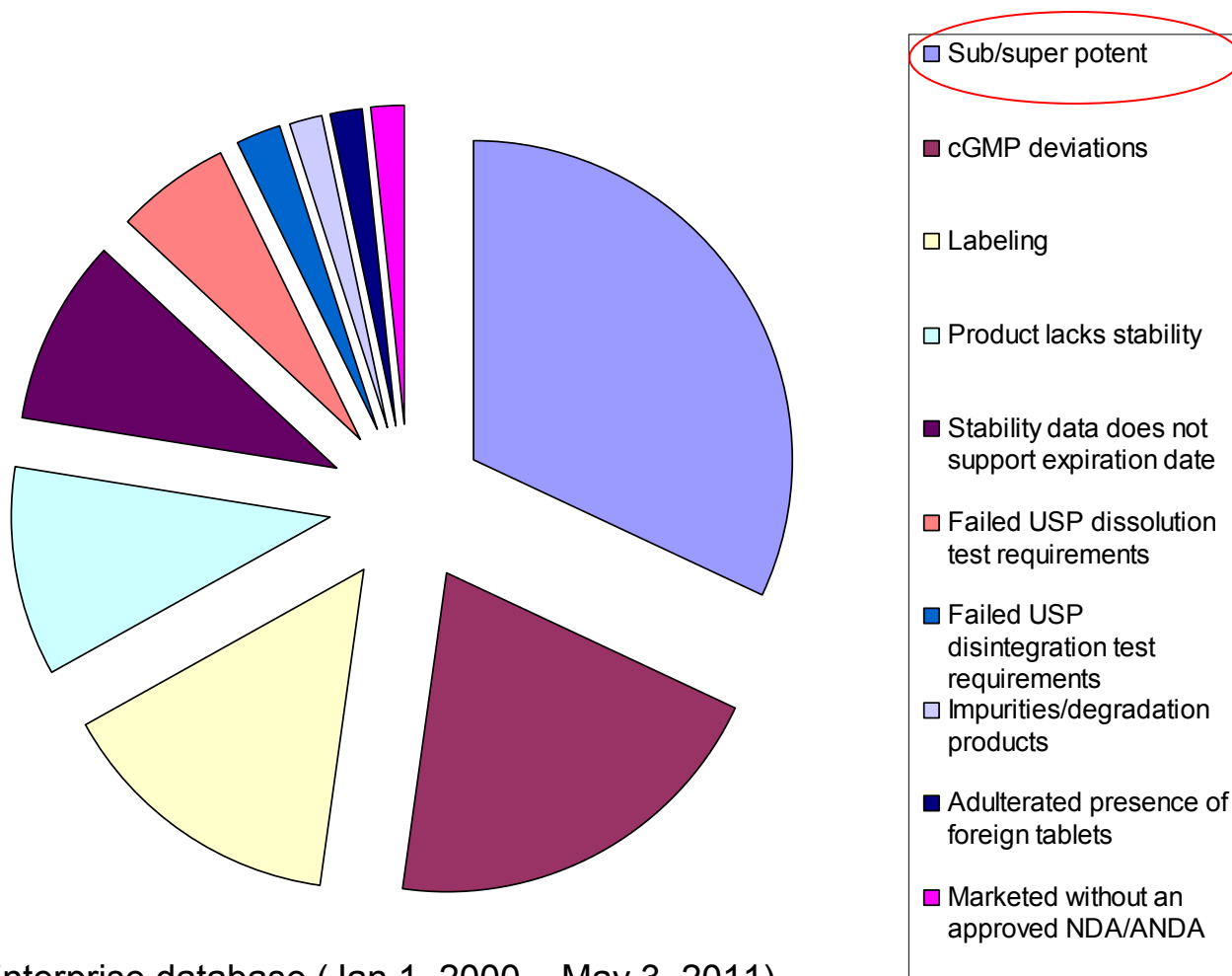
Over 80 approved and active applications

Not a comprehensive list of NTI drugs

# Quality Survey Observations

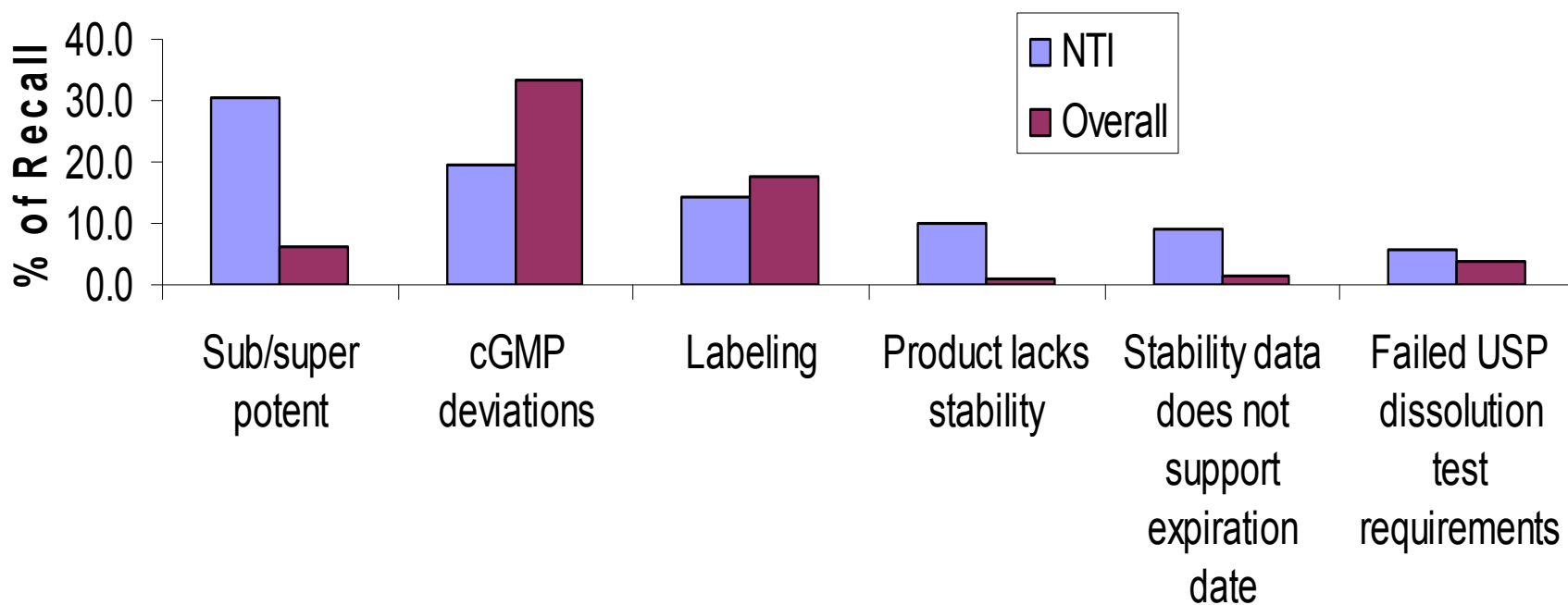
- Inactive ingredients
  - All below amounts in Inactive Ingredient Guide.
- Most surveyed NTI drug products are scored.
  - Dose strengths are as low as 0.013 mg. Some strengths are separated by  $\leq 10\%$  of drug dose.
- Manufacturing processes
  - Wet granulation process most common, followed by direct compression, and dry granulation.
- Comparable specification tests and acceptance criteria among ANDAs and NDAs
  - Assay
  - Dissolution
  - Impurities

# Top 10 Surveyed NTI Product Recall Categories Related to Pharmaceutical Quality



Data from Recall Enterprise database (Jan 1, 2000 – May 3, 2011)

# Major Recall Rates of Surveyed NTI Compared with Overall Drugs



# Potency

- Potency expressed as the quantity of active ingredient per dosage unit.

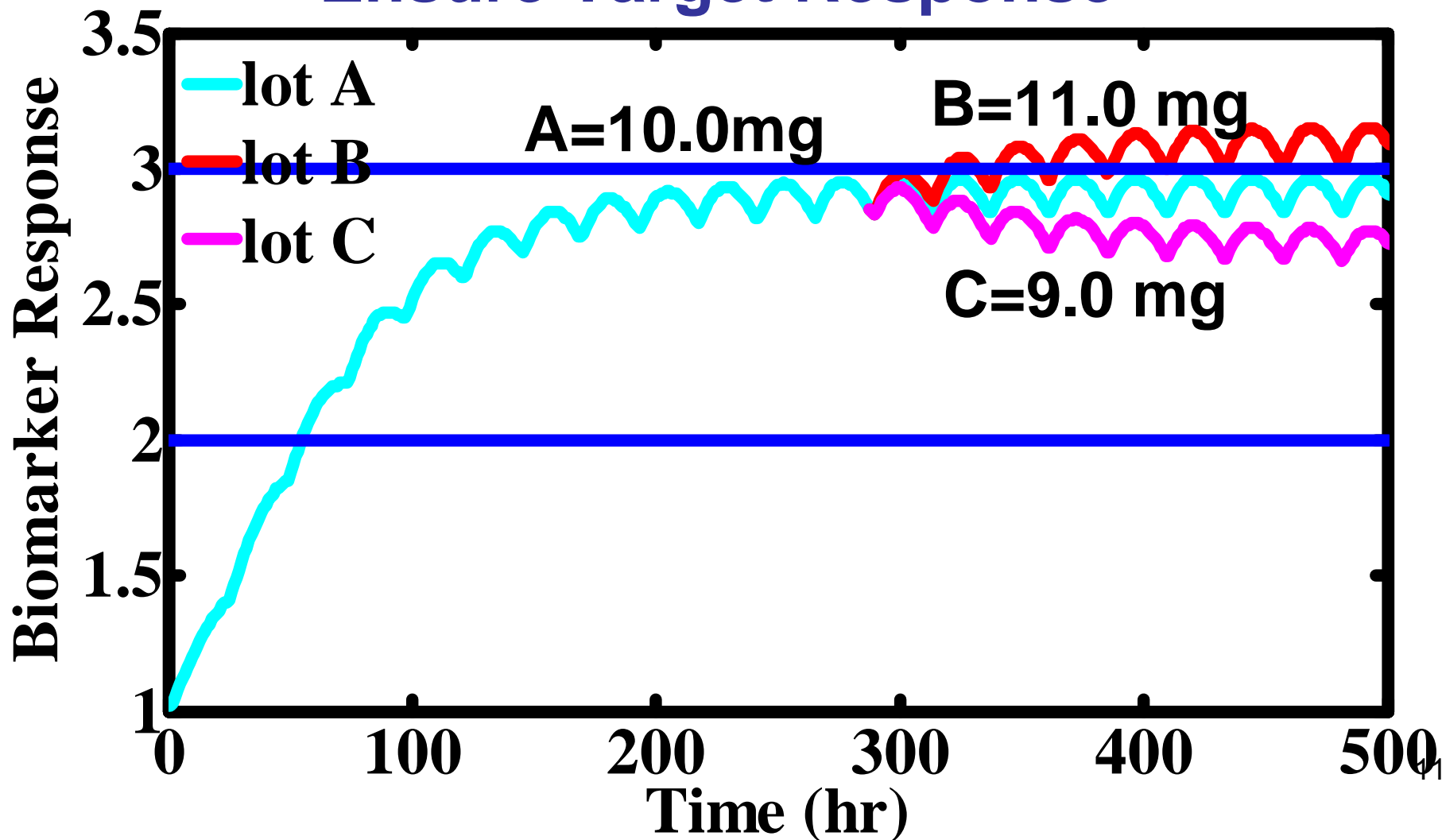
e.g., percent labeled claim (e.g., 96%), or amount of active ingredient per dosage unit (e.g., 24 mcg per tablet)

- Potency determined by assay (chromatographic, chemical determination or biological assay)

# Variable Pharmacopeia Assay Standards for NTI Drug Products

Drug products	Assay USP limits	Assay BP limits
NTI drug A Tablet	92.0-108.0%	95.0-105.0%
NTI drug A chewable tablet	93.0-108.0%	-
NTI drug A Extended release tablet	90.0-110.0%	-
NTI drug A Extended release capsule	90.0-110.0%	-
NTI drug A Suspension	90.0-110.0%	-

## Assay Limits 90.0-110.0% Insufficient to Ensure Target Response



# Assay Limits 90.0-110.0% Insufficient for NTI Drugs with Close Dose Strengths

- Tablet strengths are separated by  $\leq 10\%$  of drug dose.
- If a tablet loses 10% potency, its drug content will overlap with that of a tablet at the next lower dose strength.



# Tighter BE Limits Require Narrower Assay Limits

Drugs	Assumption	BE limits	Assay limits
Non-NTI	20% variation in pharmacokinetics (PK) won't lead to clinically relevant difference	90% CI 80-125%	90.0-110.0%
NTI	10% or lower variation in PK won't lead to clinically relevant difference	Tighter	Tighter

# Proposal to Tighten Assay Limits

For all NTI drug products, the assay limit is proposed to be:

95.0 -105.0%

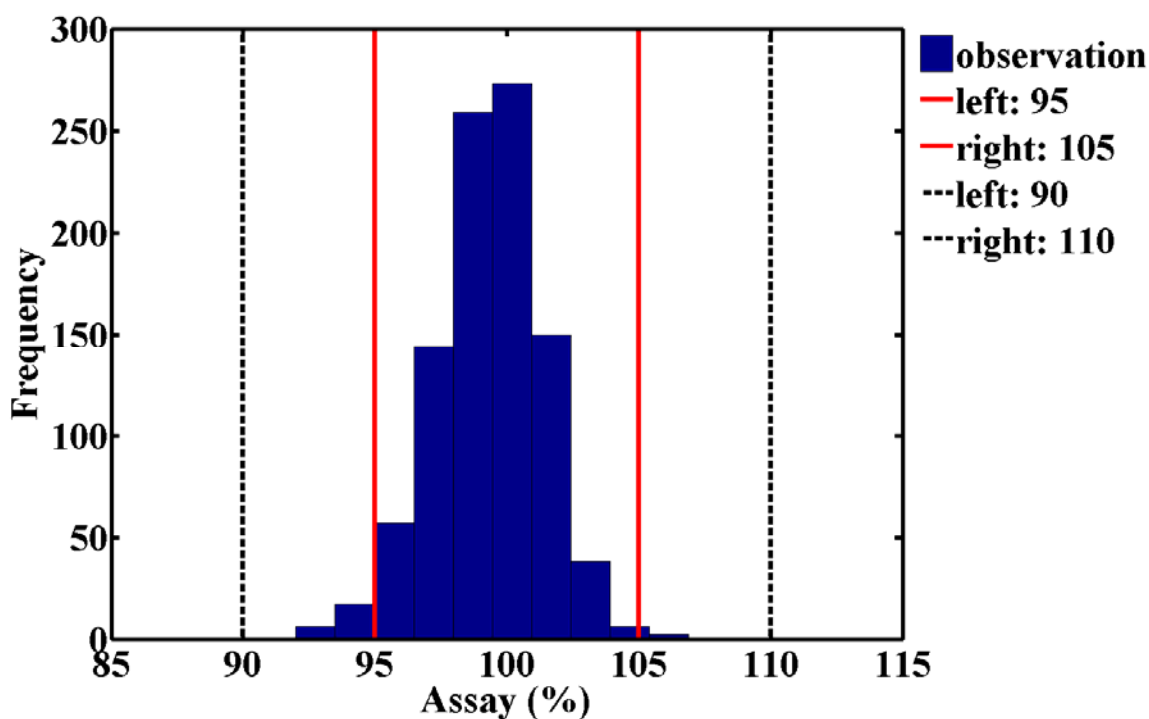
# Benefits of Tighter NTI Assay Limits

- Represent the expected clinical performance for NTI drugs
  - Small potency differences among lots, different manufacturers, and at different time during shelf life
- Consistent assay standards among different NTI drugs and dosage forms
- Prerequisite for meeting tighter bioequivalence limits

# NTI Product Quality Enhancement

- Tighter assay limits represent the expected clinical performance
- Testing against the tighter limits does not reduce the underlying variability
  - Potency failures will still be observed on stability and in market
- Quality by Design(QbD) approaches to reduce potency variability
  - Design formulation and manufacturing process
  - Monitor and update manufacturing process  
so that there is high probability to consistently provide the desired clinical performance

# Impact of Tighter Assay Limits on Approved NTIs



Average  $\pm$ SD: 99.3  $\pm$  2.2

# Conclusions

- Accurate drug dose is especially critical to NTI drug products. Drug potency issue is the No.1 reason for NTI drug product recall.
- Potential tightening of BE standards for NTI drugs necessitates tighter assay limits.
- Tightening NTI assay limits **and** utilizing QbD will have positive impacts on NTI drug product quality.

# Acknowledgements

## **Office of Compliance**

Mark Browning

Steven Wolfgang

Rick Friedman

Steven Lynn

Karthik Iyer

Israel Santiago

Catherine Gould

Elise Murphy

## **Office of Pharmaceutical Sciences (Immediate Office)**

Alex Viehmann

## **Office of Generic Drugs**

Rachelle Lubin

Kiet Nguyen

Bhawana Saluja

Feiyan Jin

Xinyuan Zhang

Lane Christensen

Robert Lionberger

Lawrence Yu



# **FDA Proposal for Bioequivalence of Generic Narrow Therapeutic Index Drugs**

*Advisory Committee for Pharmaceutical Science  
and  
Clinical Pharmacology*

*July 26, 2011*

**Barbara M. Davit, Ph.D., J.D., Acting Director  
Division of Bioequivalence 2, Office of Generic Drugs  
Center for Drug Evaluation and Research (CDER)  
United States Food and Drug Administration (US-FDA)**



# Outline

- Objectives of proposal
- Establishment of regulatory definition of narrow therapeutic index (NTI)
- Other regulatory agencies and NTI drugs
- Potency
- Study design
- Bioequivalence (BE) limits
- Summary and conclusions

# ***Objectives of proposing a new BE approach for generic narrow therapeutic index (NTI) drugs***

# Objectives of proposing a new BE approach for generic NTI drugs

- For NTI drugs, comparatively small differences in plasma concentrations may lead to serious therapeutic failures or adverse reactions
- Do we need to have a new BE approach that adds additional assurance of similarity of delivered doses and plasma concentrations following brand-generic or generic-generic switches?

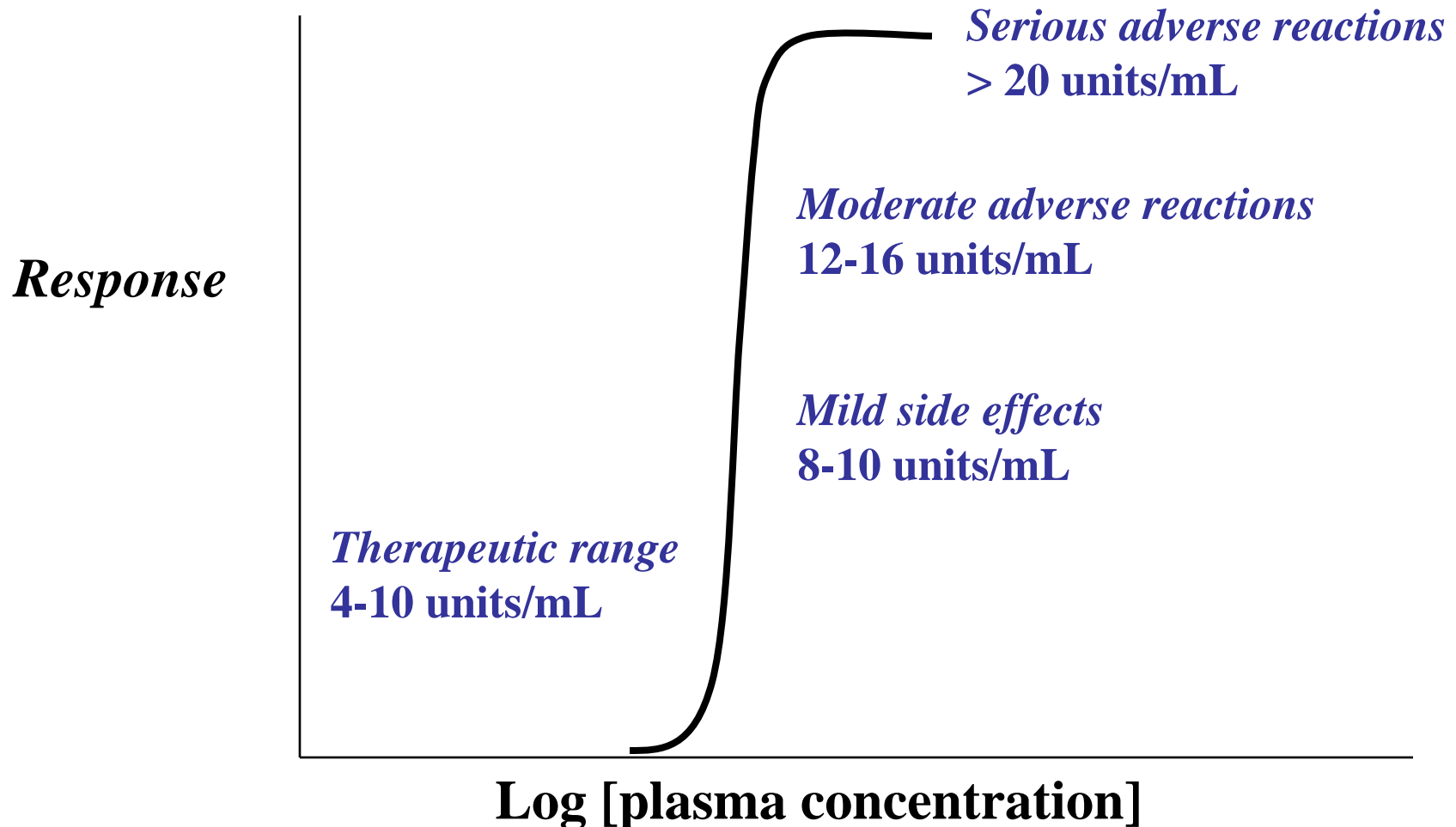


# ***Establishing a regulatory definition of NTI drugs***

# Elements of proposed regulatory definition of NTI drugs

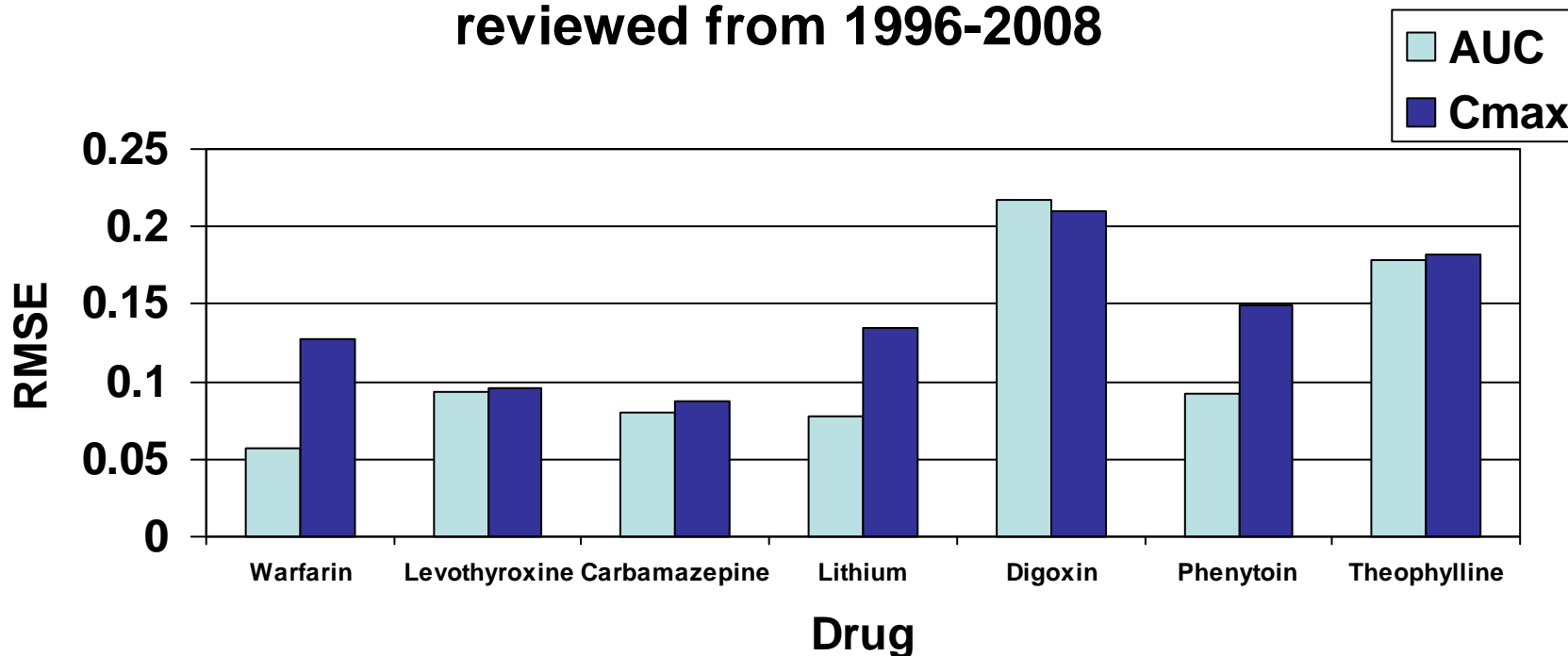
- Small differences in dose or plasma concentration may lead to serious therapeutic failures and/or adverse reactions;
- Serious events are persistent, irreversible, slowly reversible, and/or life-threatening;
- Steep dose-response curves;
- Subject to therapeutic drug monitoring;
- Small within-subject variability.

# NTI drugs have steep plasma concentration-response curves

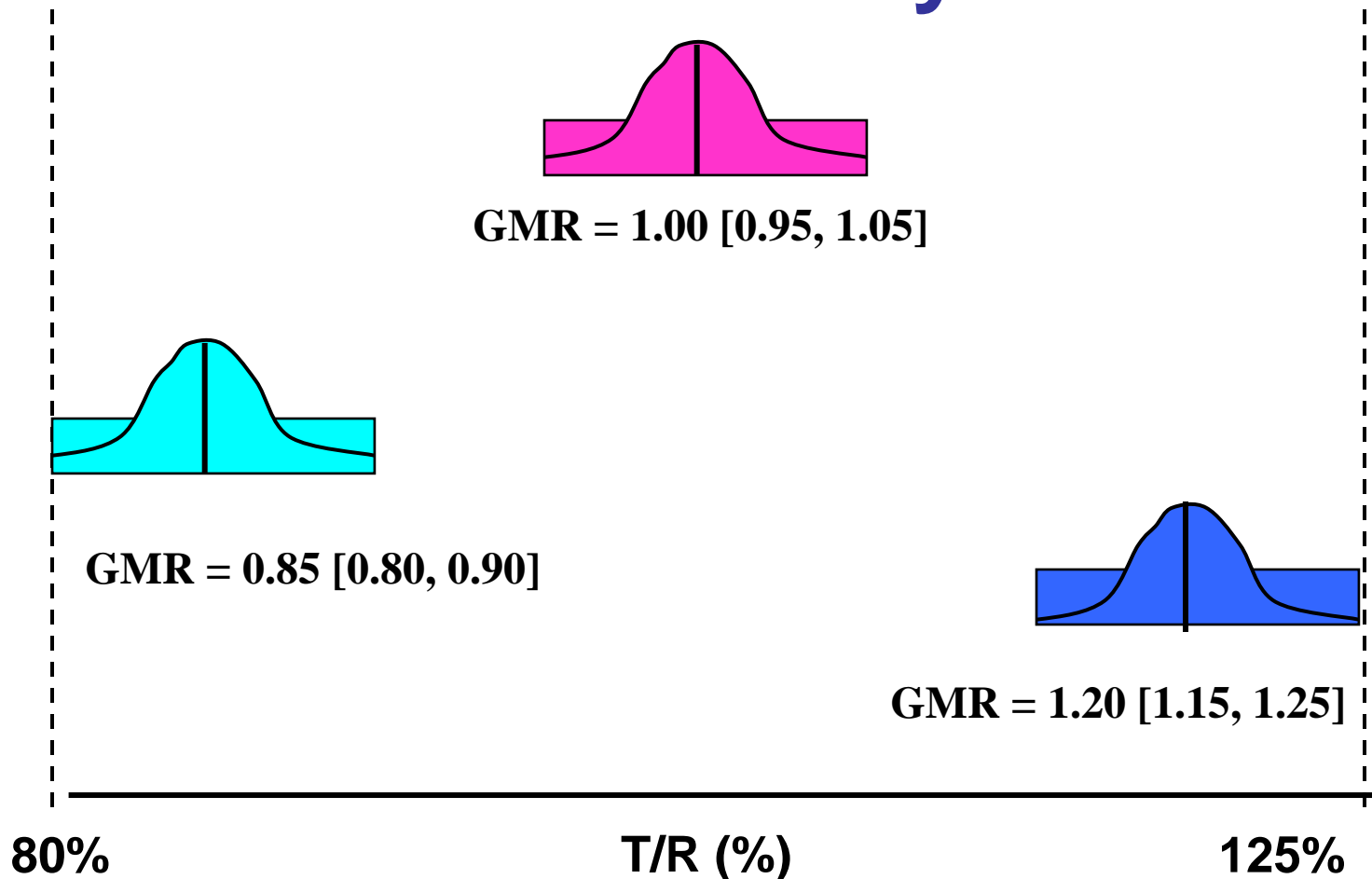


# NTI drugs generally have small within-subject variability

Average Root Mean Square Error values from 2-way BE studies of approved generic NTI drugs reviewed from 1996-2008



# Possible theoretical worst-case scenarios for BE study outcomes





# ***What do other regulatory agencies require in generic NTI drug submissions?***

## BE study acceptance criteria for generic NTI drugs

- European Union (EMA)
  - AUC: 90-111.11%
  - Cmax: 90-111.11% or 80-125%; case-by-case
- South Africa (MCC)
  - AUC and Cmax: 80-125%\*\*
  - Should not substitute generic NTI drugs unless patient adequately monitored during transition

\*\* For non-NTI drugs, BE limits for Cmax are 70-133%

## BE study acceptance criteria for generic NTI drugs (cont'd)

- Canada (Health Canada)
  - For “critical dose” drugs
  - AUC: 90-112%; C<sub>max</sub>: 80-125%
- Japan (NIHS) – AUC, C<sub>max</sub>: 80-125%
  - Compare in vitro dissolution profiles of lower strengths of test and reference products
  - If statistical tests show that test and reference dissolution profiles are not similar, then in vivo testing is necessary (no biowaiver)



# ***Potency***

# Proposed potency specifications for NTI products

- Generic versions of NTI drug products will be expected to meet assayed potency specifications of 95.0% to 105.0%
- This will assure that switching between brand-to-generic or generic-to-generic will provide comparable doses
- This will also help ensure consistency of the dose delivered throughout shelf life



# ***Recommended BE study design for NTI drugs***

## Recommended BE study design for NTI drugs

- Four-way crossover, fully replicated design
- Test product given twice
- Reference product given twice
- This design will provide the ability to
  - Scale a criterion to the within-subject variability of the reference product; and
  - Compare test and reference within-subject variances to confirm that they do not differ significantly.



# ***Recommended BE limits for generic NTI drugs***



# Recommended BE limits for generic NTI drugs

- BE limits will change as a function of the within-subject variability of the reference product (reference-scaled average bioequivalence (“reference-scaled ABE”))
- If reference variability is  $\leq 10\%$ , then BE limits are reference-scaled and are narrower than 90-111.11%
- If reference variability is  $> 10\%$ , then BE limits are reference-scaled and wider than 90-111.11%, but are capped at 80-125% limits
- This proposal encourages development of low-variability formulations

# Reference-scaled ABE approach

- T and R are considered BE if

$$\frac{(\mu_T - \mu_R)^2}{\sigma_{WR}^2} \leq \theta$$

- Where
  - $\mu_T$  and  $\mu_R$  are the means of the ln-transformed pharmacokinetic (PK) endpoint;
  - $\sigma_{WR}$  is the within-subject standard deviation (SD) of the ln-transformed PK endpoint of the reference

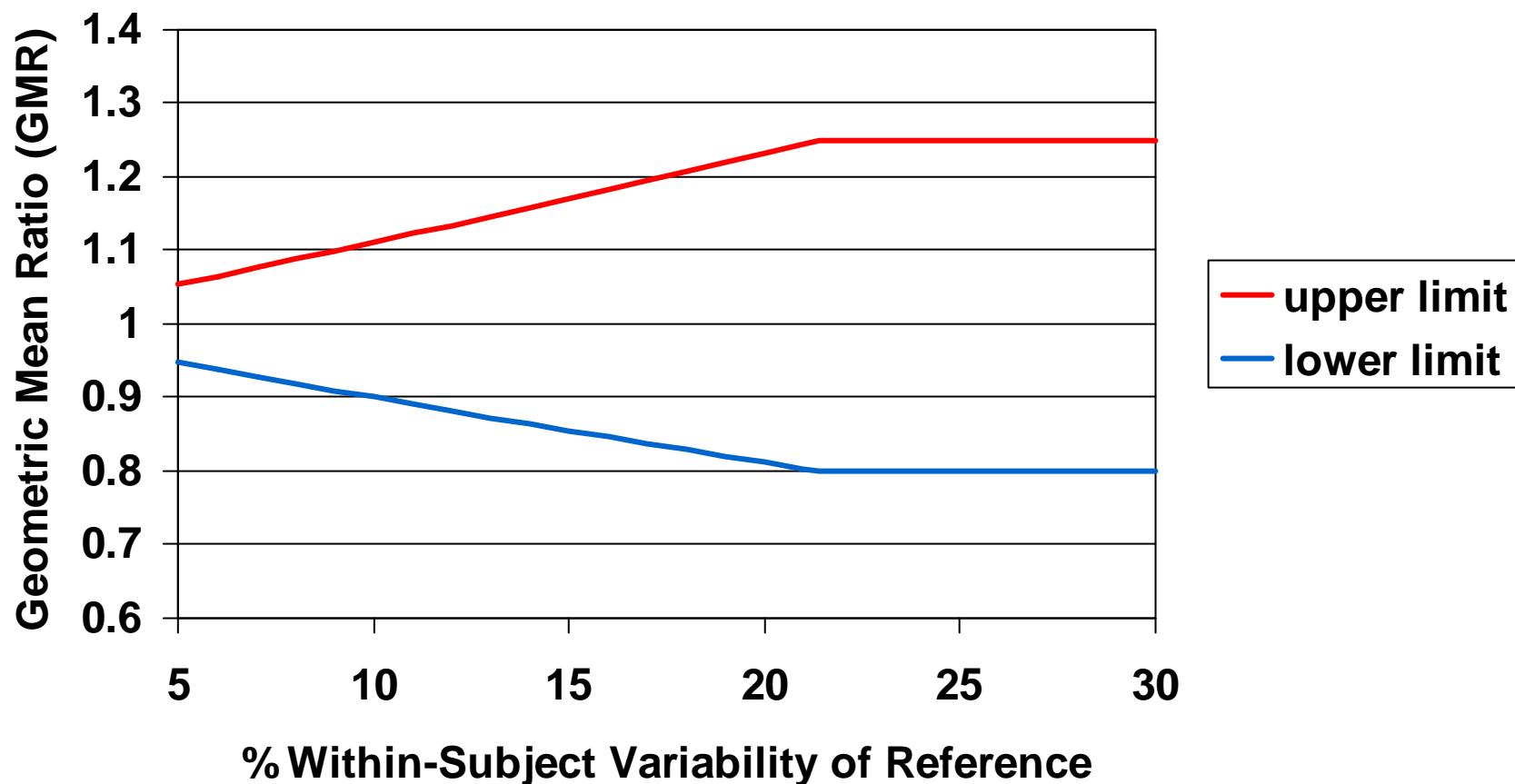
## Reference-scaled ABE (cont'd)

- The regulatory limit  $\theta$  is defined as

$$\theta \equiv \left( \frac{\ln(\Delta)}{\sigma_{W0}} \right)^2$$

- Where  $\sigma_{W0}$  is a regulatory constant
- $\Delta$  is the upper BE limit that applies when  $\sigma_{WR} = \sigma_{W0}$
- For NTI drugs, FDA proposes to set  $\sigma_{W0}$  as 0.10 and  $\Delta$  as 1.1111 (= 1.0/0.9)

## Implied BE limits on Geometric Mean (T/R) Ratios





# ***Summary and conclusions***

## Summary

- Applying a regulatory definition will permit classification of drugs which have a NTI
- Tightening potency specifications will reduce variation in delivered doses of NTI drugs upon brand-to-generic or generic-to-generic switches

## Summary (cont'd)

- Conducting 4-way fully replicated BE studies will permit comparison of test and reference AUC and Cmax variances to assure that these do not differ significantly
- Applying a reference-scaled ABE approach to analyze BE data from generic NTI drugs is more conservative and more appropriate to the PK characteristics of each NTI drug

## **Overall, we conclude that using the proposed approaches will:**

- Bring the US into harmony with other regulatory agencies who make special considerations for acceptance limits for BE studies of NTI drugs; and
- Improve public confidence in quality and switchability of generic formulations of NTI drugs.



## Acknowledgements

- Dale Conner
- Stella Grosser
- Wenlei Jiang
- Rob Lionberger
- Rachelle Lubin
- Fairouz Makhlouf
- Patrick Nwakama
- Devvrat Patel
- Don Schuirmann
- Sriram Subramaniam
- Lawrence Yu
- Xinyuan Zhang



***Thank you for your attention!***



# Quality and Safety of Generic Drug Products

*Advisory Committee for Pharmaceutical  
Science*

*and*

*Clinical Pharmacology*

*July 26, 2011*

**Keith O. Webber, Ph.D.**

**Deputy Director**

**Office of Pharmaceutical Science**

**Acting Director**

**Office of Generic Drugs**

**CDER, FDA**

# Generic Drugs

- >75% of prescriptions are filled with generics
- Cost savings is substantial (\$800M over last 10 yrs.)
- Cost differential and substitution at pharmacy limits patients' choices
- OGD serves to ensure that generic drugs are equivalent to their brand name counterparts.

# Regulations

- Generic drugs must be the same as the Reference Listed Drug
  - Active Ingredient
  - Dosage Form
  - Strength
  - Route of Administration
  - Conditions of Use
- Variances in formulation are allowable

# Quality-by-Design

- Global initiative
- Product designed with performance in mind
- Manufacturing process designed to ensure consistent product quality

# Safety Concerns

- Many safety concerns apply to brand product and generic versions
  - e.g., API – related adverse events
- Some are unique to formulation, product design, or manufacturing

# Safety Issues

- Swallowability
  - Size, Shape, Coating
- Medication errors
  - Inconsistent appearance
    - Inability to recognize dispensing errors



# Patient Compliance

- Discomfort with change
- Dissatisfaction with medicine due to:
  - Bad taste
  - Bad odor
  - Tactile unpleasant (e.g., O.D.T)
  - Size too large

# Skepticism

- Doubts about performance due to concerns with appearance or other sensory characteristics.

# OPS Activities

- Monitoring Patient Complaints
- Post-marketing Surveillance
- Laboratory Research
- Developing Standards & Regulatory Policy

# Topics

- Clinical and Safety Perspective
  - **Laurie Muldowney, MD** (Medical Officer, OPS, CDER, FDA)
- Quality Perspective
  - **Vilayat Sayeed, Ph.D.** (Director, Division of Chemistry III, OGD)
- Research Activities
  - **Mansoor Khan, Ph.D.** (Director, Div. of Pharmaceutical Quality Research, Office of Testing and Research, OPS)
- Industry Perspective
  - **Gordon Johnson** (GPhA)



# Postmarketing Drug Safety: Considerations for ANDAs

*Advisory Committee for Pharmaceutical  
Science*

*and*

*Clinical Pharmacology*

*July 26, 2011*

**Laurie Muldowney, MD**  
**OPS/CDER/FDA**

# Agenda

- Unique Safety Considerations for Generic Drugs
- Evolving OGD Postmarketing Process
- Clarifying Questions

# Background

- FDAAA
  - Increasing emphasis on postmarketing surveillance
  - Safety First Initiative
- Generic skepticism
  - Need for a process whereby we specifically evaluate generic drug products during the postmarketing period

# Public Skepticism about Generics

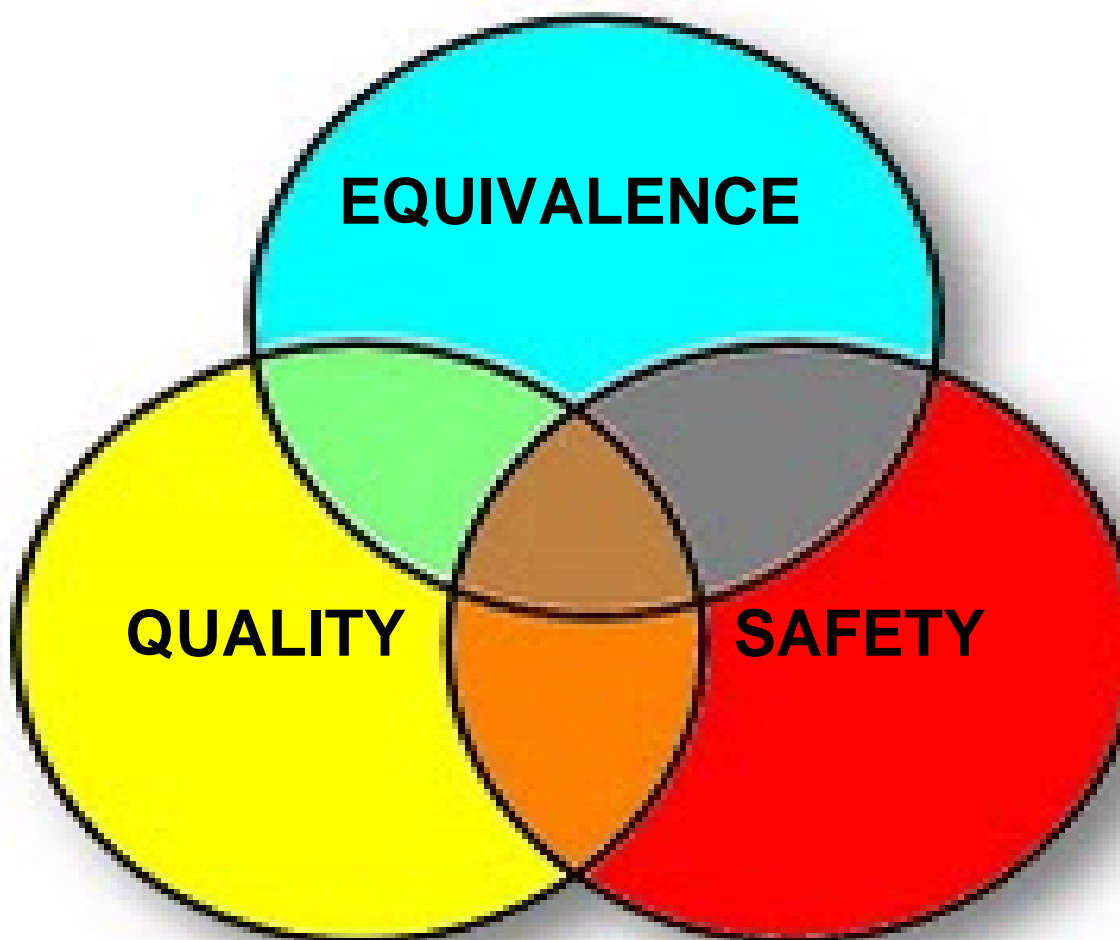
- Perception that generic products don't work as well as the brand products
  - Frequent perception that more expensive is better
  - Lack of understanding of the generic approval process
  - Historical
- Worsening symptoms after switch to therapeutically equivalent product often attributed to a faulty generic
- May be related in part to experiences with different generic drug characteristics
  - Different appearance from RLD and other generics



# Postmarketing Safety Considerations in ANDAs

- Unique needs and challenges for generic drug products
- Emphasis on manufacturer specific quality, safety, and equivalence issues
  - Formulation differences
  - Manufacturing process quality assurance
  - Bioequivalence questions
- Less focus on safety issues related to the active ingredient
  - OSE/OND focus
- Focus is not limited to serious, unlabeled adverse events

# Generic Drugs Postmarketing Surveillance



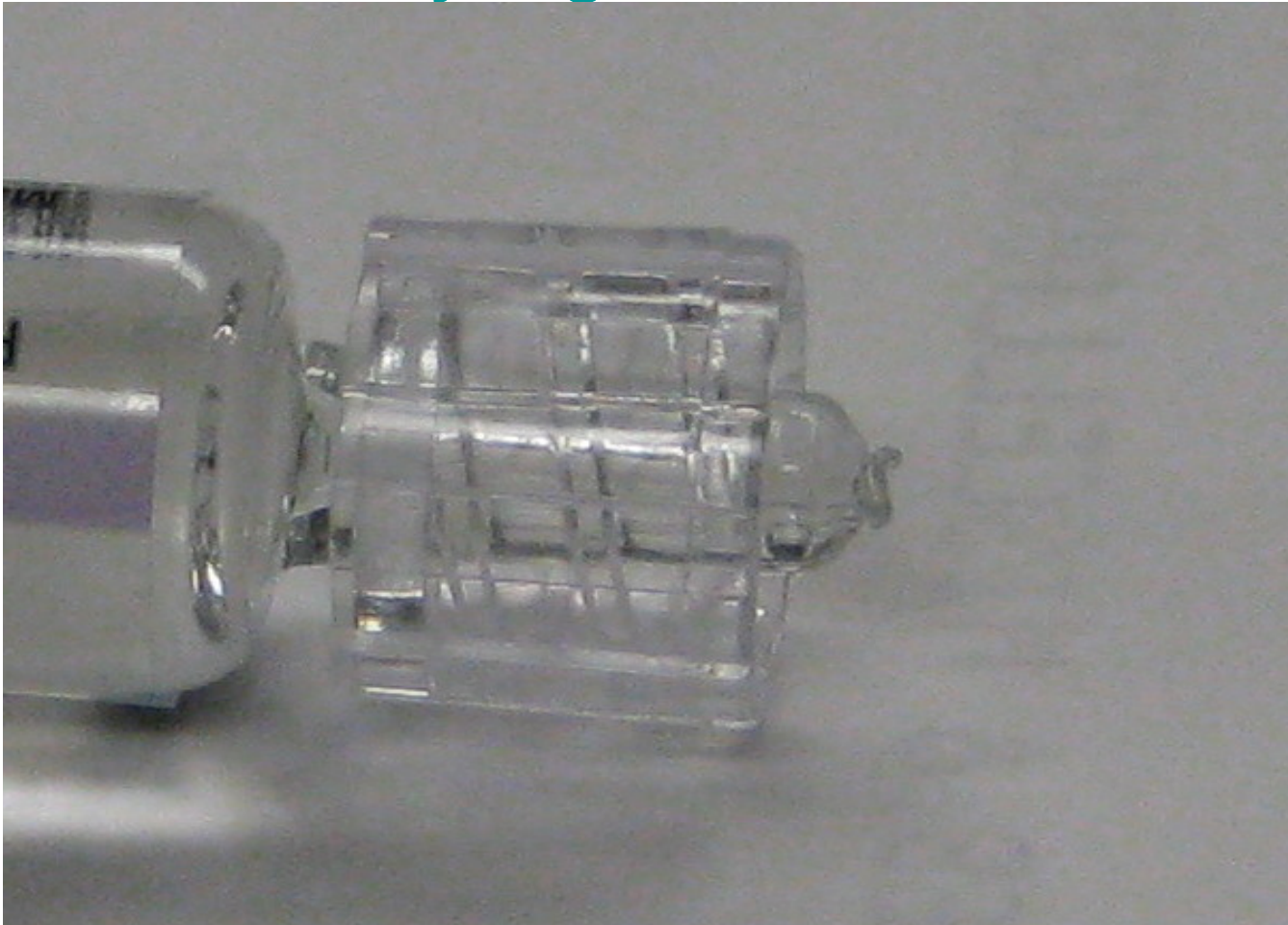
# Quality Issues and Complaints: Examples

## Patch won't stick



# Quality Issues and Complaints: Examples

## Syringe failures



# Quality Issues and Complaints: Examples

## Labeling problems: Missing lot and exp. date





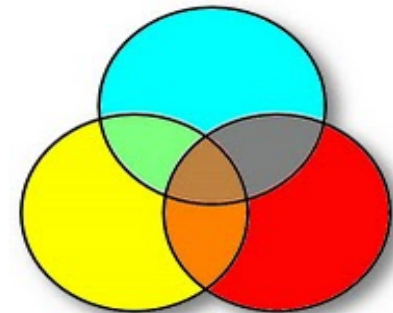
# Quality Issues and Complaints: Examples

**Many complaints about ODOR and TASTE!**



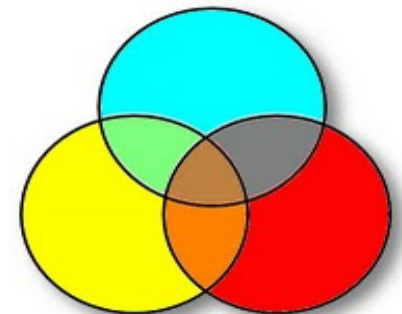
# Examples of Quality Issues that May Lead to Safety Issues

- A larger tablet may be more difficult to swallow
- A tablet that disintegrates quickly or sticks to a moist surface may be difficult to swallow
- A tablet coating may be needed to mask a bad taste or odor, to keep the tablet intact until it is swallowed, or to protect the esophagus from an irritating drug substance
- A transdermal patch that doesn't stick will not be effective



# Therapeutic Equivalence (TE)

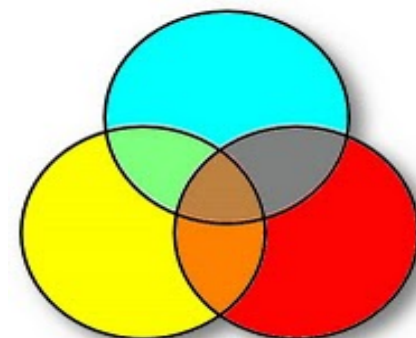
- *Pharmaceutical equivalents*: contain the same active ingredient(s), are of the same dosage form, route of administration and are identical in strength or concentration
- *Therapeutic equivalents*: pharmaceutical equivalents and **can be expected to have the same clinical effect and safety profile** when administered to patients under the conditions specified in the labeling.
- Therapeutically equivalent products must meet the following general criteria:
  - Approved as safe and effective;
  - Pharmaceutical equivalents;
  - Bioequivalent
  - Adequately labeled;
  - Manufactured in compliance with Current Good Manufacturing Practice regulations





# Therapeutic Inequivalence

- *“I switched to generic x and it didn’t work like the brand name product”*
  - TE products are expected to have the same clinical effect and safety profile
- Quality issues can affect equivalence
- Formulation differences? BE issues?
- Challenging to interpret
  - Anecdotal, low reporting rates
  - Generic skepticism
  - Nocebo effect, Weber effect
  - Poor quality of reports



# Goals of OGD Postmarketing Surveillance

1. Determine whether allowable differences between the generic product and the RLD have changed the safety or efficacy profile of the product
2. Ensure manufacturer specific quality assurance through collaboration with OC
3. Apply new understanding to future premarket reviews

# CURRENT OGD Postmarketing Surveillance Process

- Postmarketing Surveillance Team
  - Responsible for initial triage and tracking of potential safety issues
- Bimonthly Postmarketing Surveillance Meetings
  - Larger group including multiple CDER office representations
  - Responsible for initial assessment of potential safety signals and recommendations for further evaluation/action
- Safety First Processes
  - Utilize existing processes and procedures for tracking, evaluating, and communicating about potential safety issues

# OGD Postmarketing Surveillance Team

- Multidisciplinary team within OGD which addresses emerging safety and quality issues in OGD
- Focal point for information from various offices pertaining to safety issues which impact generic products
- Initiates evaluation and tracking of reports of inferior product quality, adverse events, and different therapeutic effect compared with RLD
- Works collaboratively with other CDER offices when potential issues are identified as requiring further investigation

# Data Sources/Signal Generation

- DQRS
  - Field Alert Reports (FARs)
  - Spontaneous MedWatch reports through DQRS:
    - Quality complaints (quality only issues and quality issues leading to adverse events)
    - Direct reports of unexpected therapeutic effects after switching
- AERS
- Spontaneous reports sent directly to OGD
- Published literature
- Consumer groups and other sources
- Future considerations/opportunities:
  - Data mining strategies
  - Distributed databases (e.g. Sentinel System)
  - Optimizing FAERS

# Evaluation/Management of Potential Signals

- Initial evaluation
  - Compare formulations/BE study results
  - AERS search
  - Manufacturing information
- Discuss at bimonthly postmarketing surveillance meeting
- Determine need for further evaluation

# Evaluation/Management of Potential Signals (continued)

- OTR studies
- Official consult to OSE for safety/drug utilization analysis
- Communication/exchange of information with firm
- Utilize existing processes created through Safety First
  - Create DARRTS Tracked Safety Issue (TSI)
  - Establish Safety Issue Team for significant safety issues
  - Issue Drug Safety Communications, as indicated
- Collaborative studies/postmarketing research with outside partners

## Possible Outcomes from Postmarket Reviews

- No action indicated
- Change in product rating (e.g. from AB to BX)
- Request reformulation
- Development of guidance or policy
- Product withdrawal from marketplace



# Ongoing Postmarketing Research: AEDs

- Background:
  - Agency receives occasional spontaneous AE reports of therapeutic inequivalence for antiepileptic drugs (AEDs)
  - Significant skepticism related to the therapeutic equivalence of these drug products
  - Several epilepsy organizations express concerns about the interchangeability of AEDs
- Objective:
  - Assess whether an FDA approved generic epilepsy drug is bioequivalent to the innovator product (and other relevant generics) in epilepsy patients under clinical use conditions

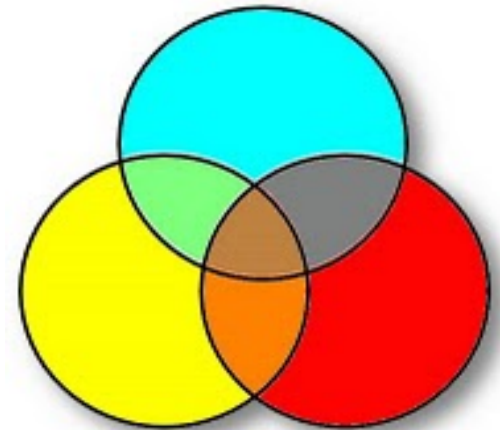
## Ongoing Postmarketing Research: AEDs (continued)

- Contract awarded to University of Maryland
  - Conduct a prospective, randomized, blinded, four period replicate crossover steady-state study to determine if generic lamotrigine 100 mg is bioequivalent to RLD in epilepsy patients
- Additional studies planned to compare BE with generic to generic switches

## *Orally Disintegrating Tablet*

Received reports that a specific manufacturer's orally disintegrating tablet had clogged and blocked oral syringes and feeding tubes, when the drug was administered as a suspension through these devices

- Collaborative evaluation
  - DQRS search, AERS search, search of periodic safety reports
  - OGD Science Team evaluation of formulation
  - OSE drug utilization information
  - OTR testing
  - OC facilitated meetings with manufacturer
- Created TSI (through OSE)
- Voluntary Market Withdrawal
- Communication with Stakeholders





**U.S. Food and Drug Administration**  
Protecting and Promoting Public Health

[www.fda.gov](http://www.fda.gov)

# Questions?



# Equivalence by Design - Consumer Concern

*Advisory Committee for Pharmaceutical Science  
and  
Clinical Pharmacology*

*July 26, 2011*

**Vilayat A. Sayeed, Ph.D.**  
**Director, Division of Chemistry III**  
**Office of Generic Drugs**

## ICH Q8(R2)- Quality by Design

- Systematic approach to development
- Emphasizes product and process understanding and process control
- Based on sound science and quality risk management
- Begins with predefined objectives

# Predefined Objectives

## Quality Target Product Profile

- Active Pharmaceutical Ingredient
- Product Strength
- Dosage Form
- Route of Administration
- Labeling (conditions of use)
- Performance
- Quality
- BA/BE

# **Predefined Objectives Overlooked**

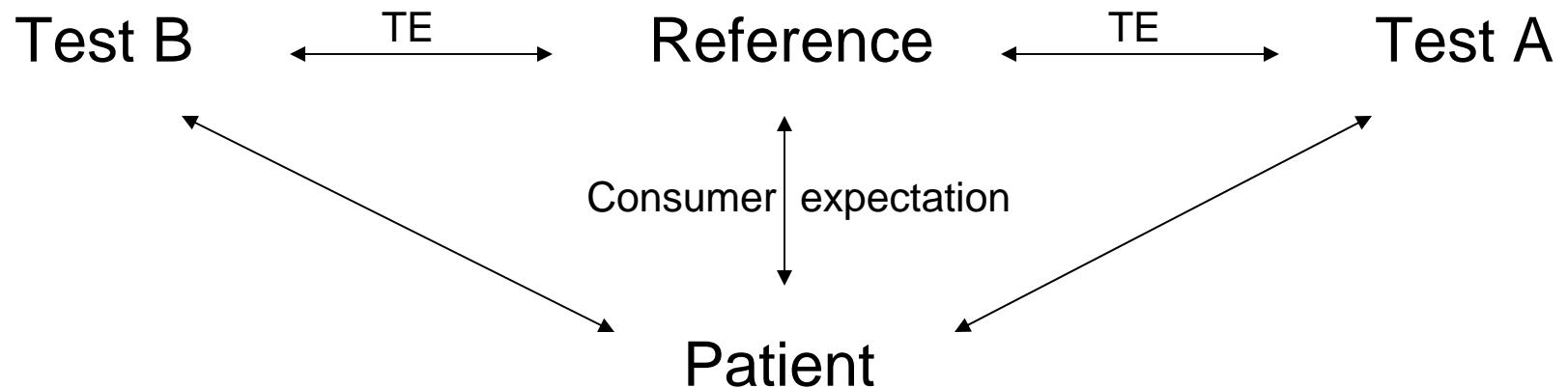
## **Quality Target Product Profile**

### **Issues of Concern**

- Beads in capsule shell
- Tablet size, shape and color
- Tablet score - Ease of splitting
- Taste and odor masking and tablet dust (coated vs. uncoated)



## Why are these objectives critical?



# Predefined Objectives Overlooked

## Beads/Powder in capsule shell

- Reference has beads – Test has mini tablet
  - Published draft guidance (addresses condition of use concerns)
- Capsule products not covered by use condition
  - Include this in PD strategy to address consumer compliance

# Predefined Objectives Overlooked

## Tablet size, shape and color

- Test substantially larger than RLD for same strength
- Shape in combination with size can be an issue
  - A draft guidance will be issued soon
- Same size, shape and color for all strengths

# Predefined Objectives Overlooked

## Tablet Score – Ease of Splitting

- Uneven breaking
- Crumbles upon splitting
- Content distribution concerns (in-house data)
  - A draft guidance will be issued soon



# **Predefined Objectives Overlooked**

## **Taste and odor masking and tablet dust**

- Design and process difference
- Reference non-function coat, test uncoated

# Predefined Objectives Overlooked

## Office Focus

- Pay attention to physical and organoleptic properties of reference in test development
- Look from consumer perspective and potential for non-compliance

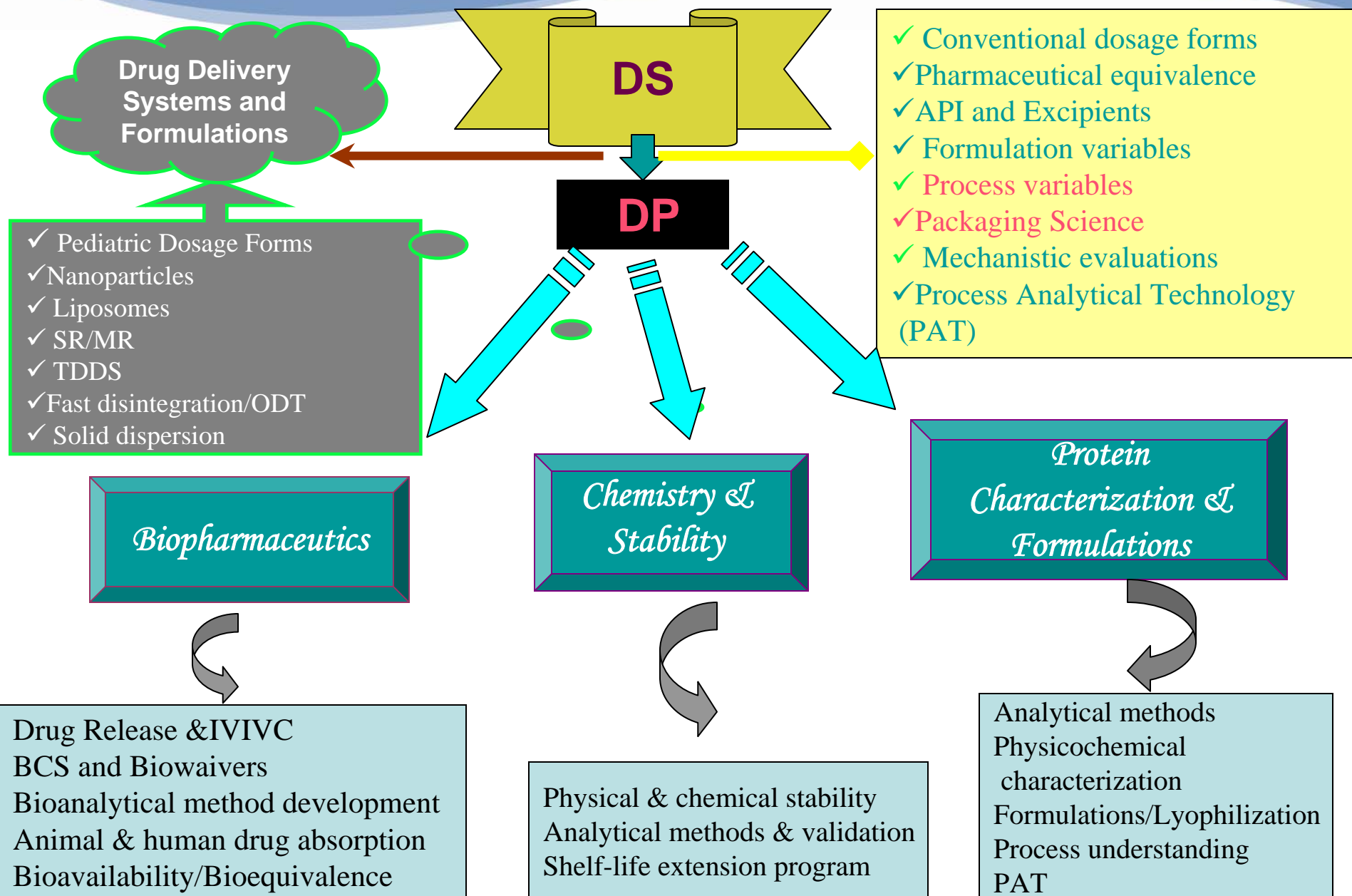


# **Division of Product Quality Research (DPQR): Regulatory Research to Support the Office of Generic Drugs**

*Advisory Committee for Pharmaceutical Science  
and  
Clinical Pharmacology*

*July 26, 2011*

**Mansoor A. Khan, R.Ph., Ph.D.  
Director, OPS/OTR/DPQR**





# Stability Studies

- Applicant conducts systematic stability testing (21 CFR 211.166) according to a prescribed protocol
  - Select samples from representative batches
  - Store samples at defined storage conditions
  - Accelerated (40°C/75% relative humidity or RH)
    - Long-term (25°C/60% RH)
    - Intermediate (30°C/65% RH), if needed

Pull samples at predetermined intervals

http://www.google.com/search?hl=en&safe=active&biw=1001&bih=551&q=gabapentin+recall&aq= Live Search

File Edit View Favorites Tools Help

hp Y! Web Search Bookmarks Settings BN BN Bookstore HP Solutions HP Free Templates

Web Images Videos Maps News Shopping Gmail more Sign in

**Google**

**gabapentin recall** Search SafeSearch strict

About 840,000 results (0.14 seconds) Advanced search

**Everything**  
Images  
Videos  
News  
Shopping  
More

**White Oak, MD**  
Change location

Show search tools

**Generic Firm Commences Gabapentin Recall Due to Excessive Impurities**  
Nov 16, 2007 ... Ranbaxy Pharmaceuticals initiated a voluntary Class III **recall** of 73 million **gabapentin** tablets because the allowed level of impurities in ...  
[www.fdanews.com](#) > ... > [FDAnews Drug Daily Bulletin](#) - Cached - Similar

**India's Ranbaxy recalls gabapentin tablets in U.S. | Reuters**  
Nov 15, 2007 ... MUMBAI, Nov 16 (Reuters) - Indian drugmaker RanbaxyLaboratories Ltd is recalling some **gabapentin** tabletsin the United States, ...  
[www.reuters.com/article/.../ranbaxy-recall-idUSBOM996220071116](#) - Cached

**Gabapentin 100 mg capsules (Neurontin) - Recall**  
Jan 8, 2008 ... Alert - **Gabapentin** 100 mg capsules (Neurontin) - Recall.  
[healthcare.utah.edu/pharmacy/alerts/79.html](#) - Cached - Similar

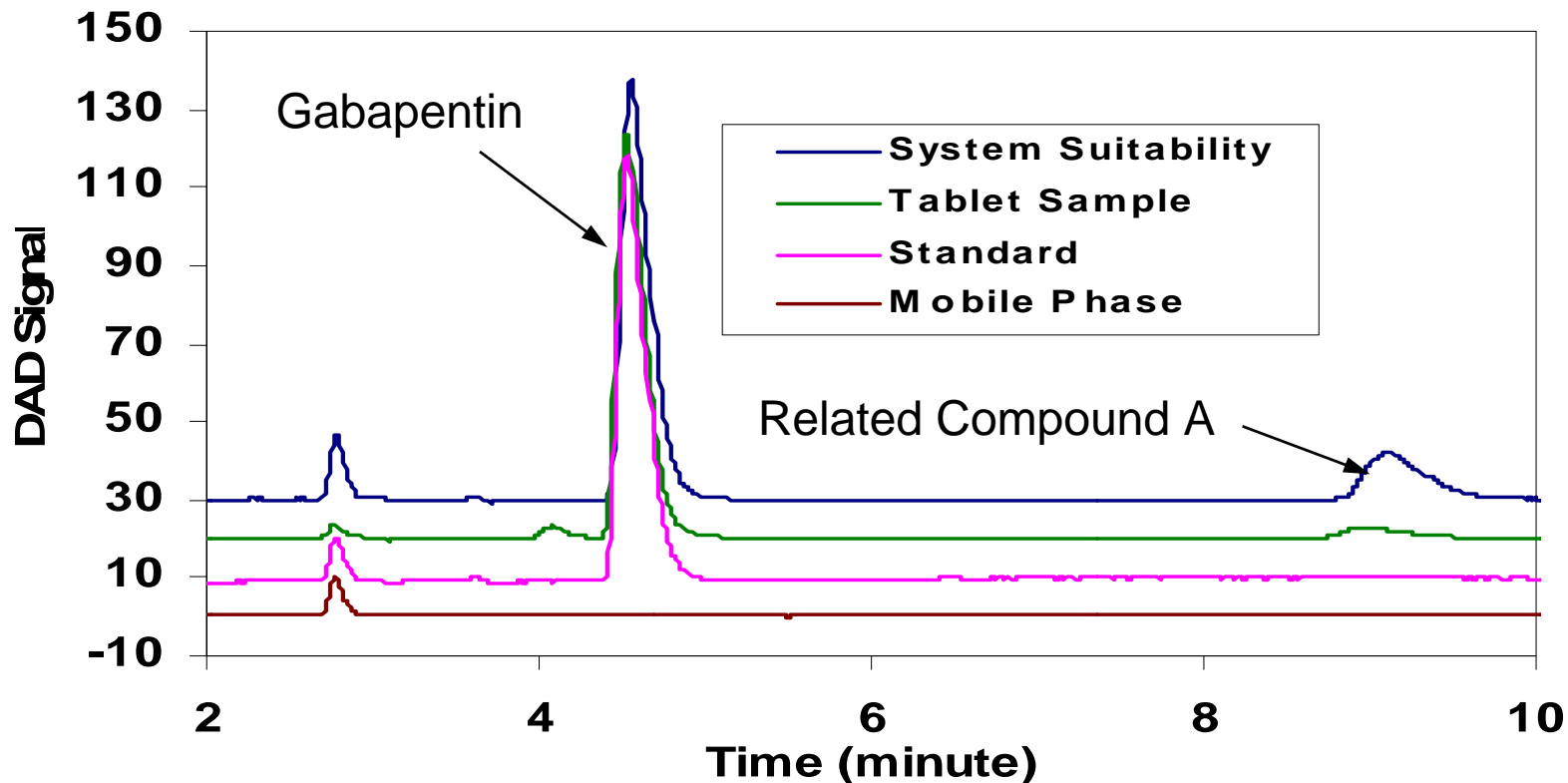
**News : MHRA batch recall: Gabapentin 300mg capsules (Teva)**  
MHRA batch **recall**: **Gabapentin** 300mg capsules (Teva). 22nd December 2010. Teva UK Ltd are recalling all remaining stock of the following batches of ...  
[www.palliatedrugs.com/.../mhra-batch-recall-gabapentin-300mg-capsules-teva-.html](#) - Cached

**Gabapentin recall - Epilepsy Forum**  
2 posts - 2 authors - Last post: Dec 29, 2007  
Quote : Last month, Ranbaxy Pharmaceuticals announced a voluntary **recall** of 73 million tablets of its epilepsy and nerve pain drug, ...  
[www.coping-with-epilepsy.com](#) > ... > [Peer Support](#) > [The Library](#) - Cached

[News] Contamination Responsible for Tevamax Recall - 1 post - Apr 19, 2011

Internet 100% 4:09 PM

# FDA Study on Gabapentin

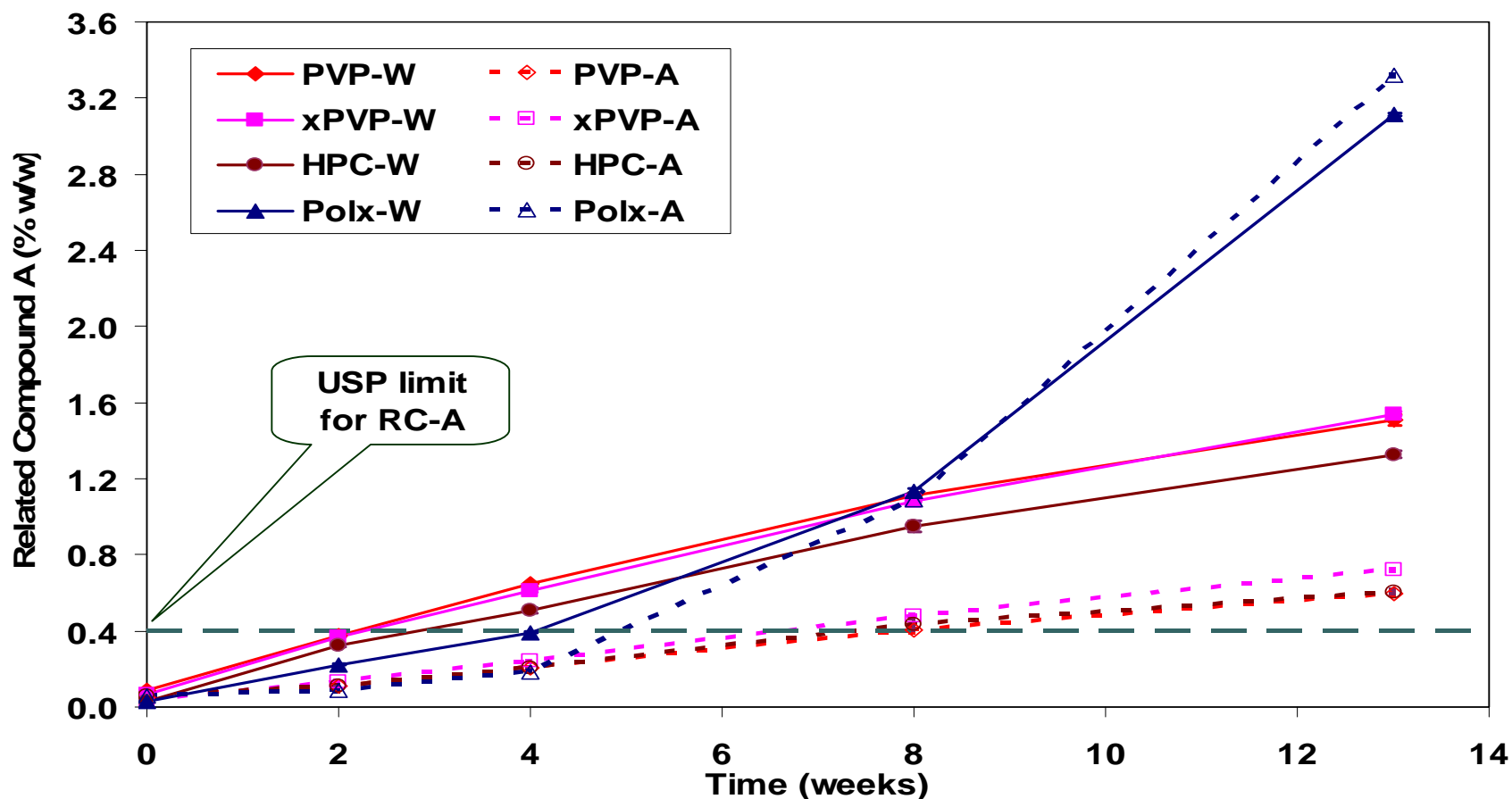


Int J Pharm. 2008 Feb 28;350(1-2):65-9

J Pharm Biomed Anal. 2008 Jan 7;46(1):181-6

J Pharm Biomed Anal. 2007 Apr 11;43(5):1647-53

## RC-A Formation in Tablets at 40 °C/75% RH



# Stability of Marketplace Generic Products

- Evaluated several products in the market as follows:
  - Determined products quality attributes such as assay/potency and dissolution with approved and validated methods.
  - About six months before the expiration date, the products were placed in stability chambers at 25°/60% RH and analyzed for assay/potency and dissolution for three months.
- Bioequivalence study with one product is in progress.

## Potency and Stability of Bupropion Tablets

Product	Bupropion Amount Found/Tablet (mg) $\pm$ SD (% Labeled Strength $\pm$ SD)			
	Time in chamber (months)			
	0	1	2	3
Product 1	300 $\pm$ 0.6 (100 $\pm$ 0.2)	298.0 $\pm$ 2.7 (99.37 $\pm$ 0.9)	302.0 $\pm$ 2.6 (100.7 $\pm$ 0.9))	300.4 $\pm$ 2.3 (100.1 $\pm$ 0.8)
Product 2	302 $\pm$ 0.2 (100.7 $\pm$ 0.1)	297.9 $\pm$ 3.3 (99.3 $\pm$ 1.1)	300.9 $\pm$ 3.7 (100.3 $\pm$ 1.2)	300.1 $\pm$ 0.8 (100.0 $\pm$ 0.3)
Product 3	304 $\pm$ 2.5 (101.3 $\pm$ 0.8)	301 $\pm$ 3.5 (100.3 $\pm$ 1.2)	298 $\pm$ 6.1 (99.3 $\pm$ 2.0)	298 $\pm$ 0.6 (99.3 $\pm$ 0.2)
Product 4	304 $\pm$ 1.1 (101.3 $\pm$ 0.4)	302 $\pm$ 3.9 (100.7 $\pm$ 1.3)	333 $\pm$ 1.7 (101.0 $\pm$ 0.6)	301 $\pm$ 0.4 (100.3 $\pm$ 0.1)

Impurities – None detectable



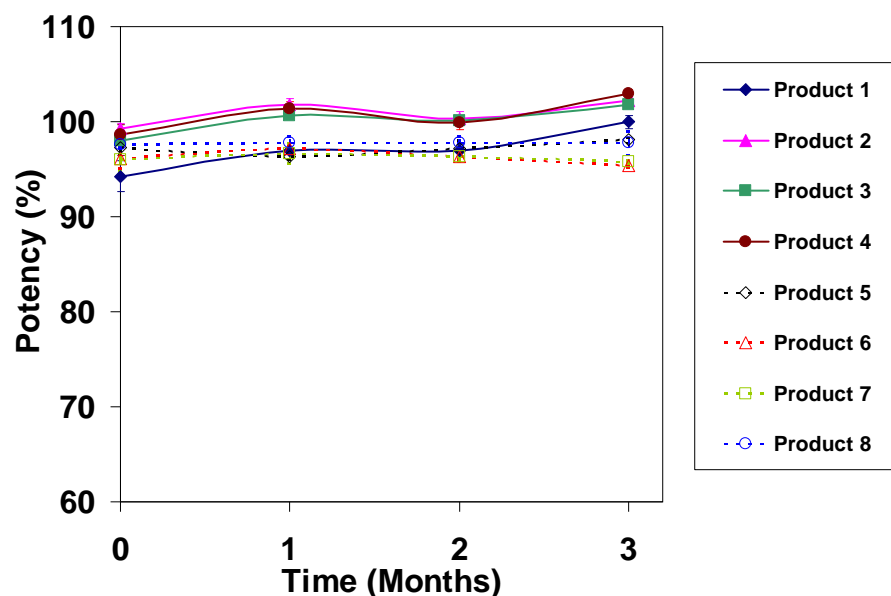
## Dissolution and Stability of Bupropion Tablets

Product	Bupropion Amount Dissolved (%) $\pm$ SD at 16 hrs			
	Time in chamber (months)			
	0	1	2	3
Product 1	101.57 $\pm$ 2.79	101.81 $\pm$ 0.87	100.63 $\pm$ 1.27	102.04 $\pm$ 1.27
Product 2	97.82 $\pm$ 0.97	99.11 $\pm$ 1.02	99.81 $\pm$ 1.39	99.13 $\pm$ 0.85
Product 3	94.32 $\pm$ 3.25	93.97 $\pm$ 1.59	90.09 $\pm$ 1.36	94.32 $\pm$ 1.91
Product 4	101.56 $\pm$ 1.29	99.81 $\pm$ 0.43	96.29 $\pm$ 0.97	100.87 $\pm$ 1.81

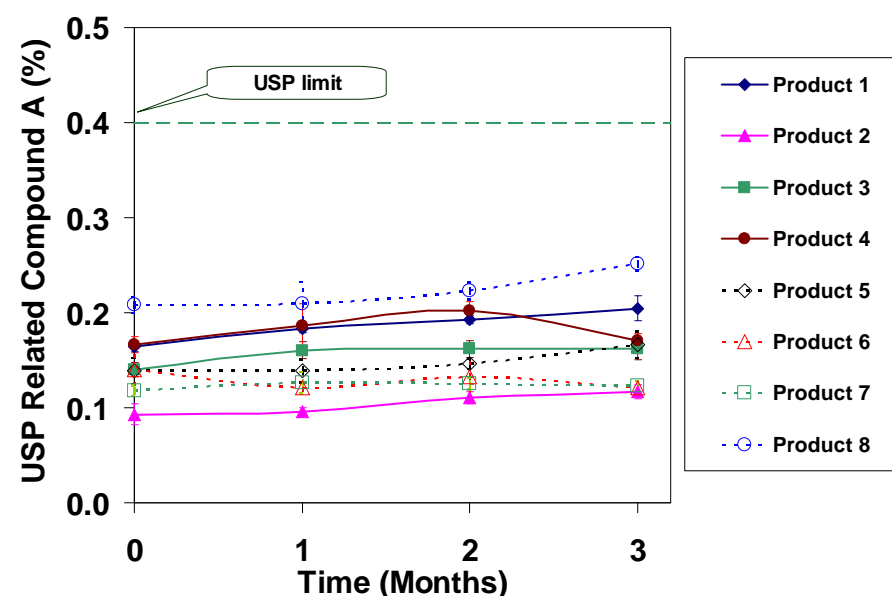
USP Tolerance for Amount Dissolved (%) at 16 hrs is: NLT 80%

# Potency and Stability of Eight Gabapentin Tablet Drug Products

## Potency



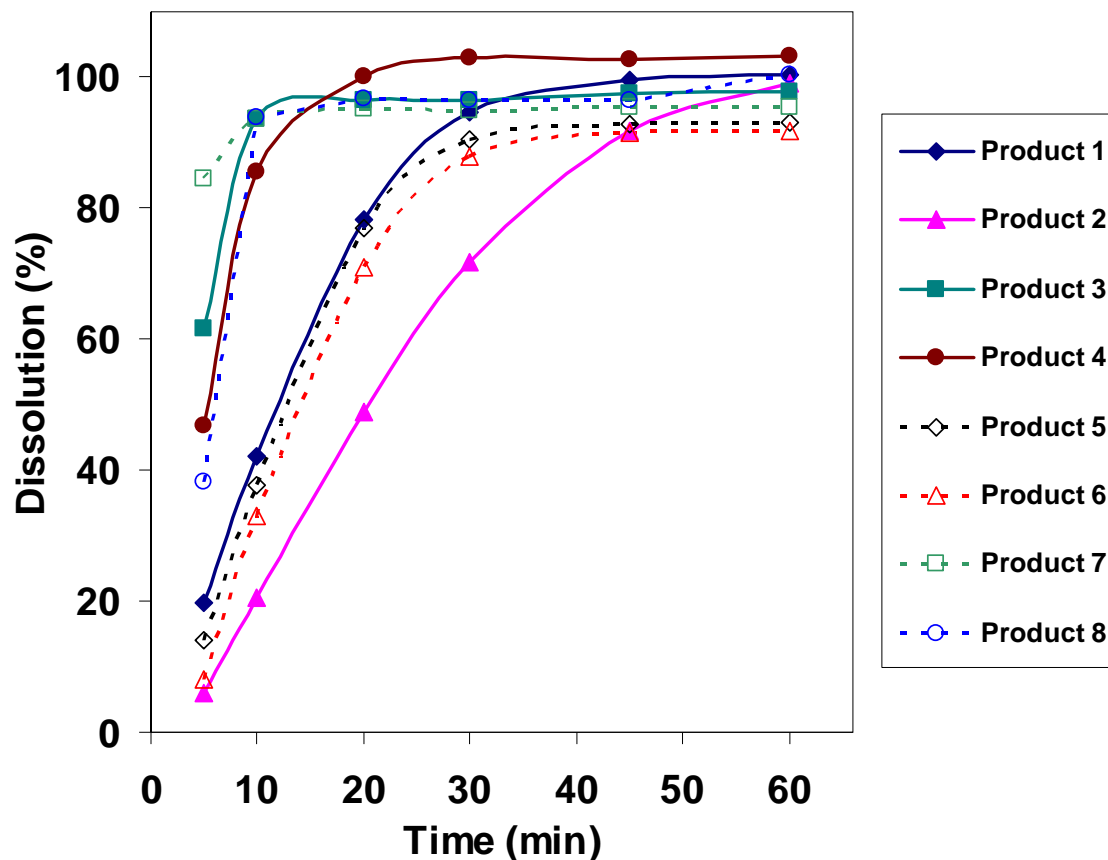
## Stability



All samples met the compendial requirements when stored under ICH long-term storage conditions (25 °C/60% RH)

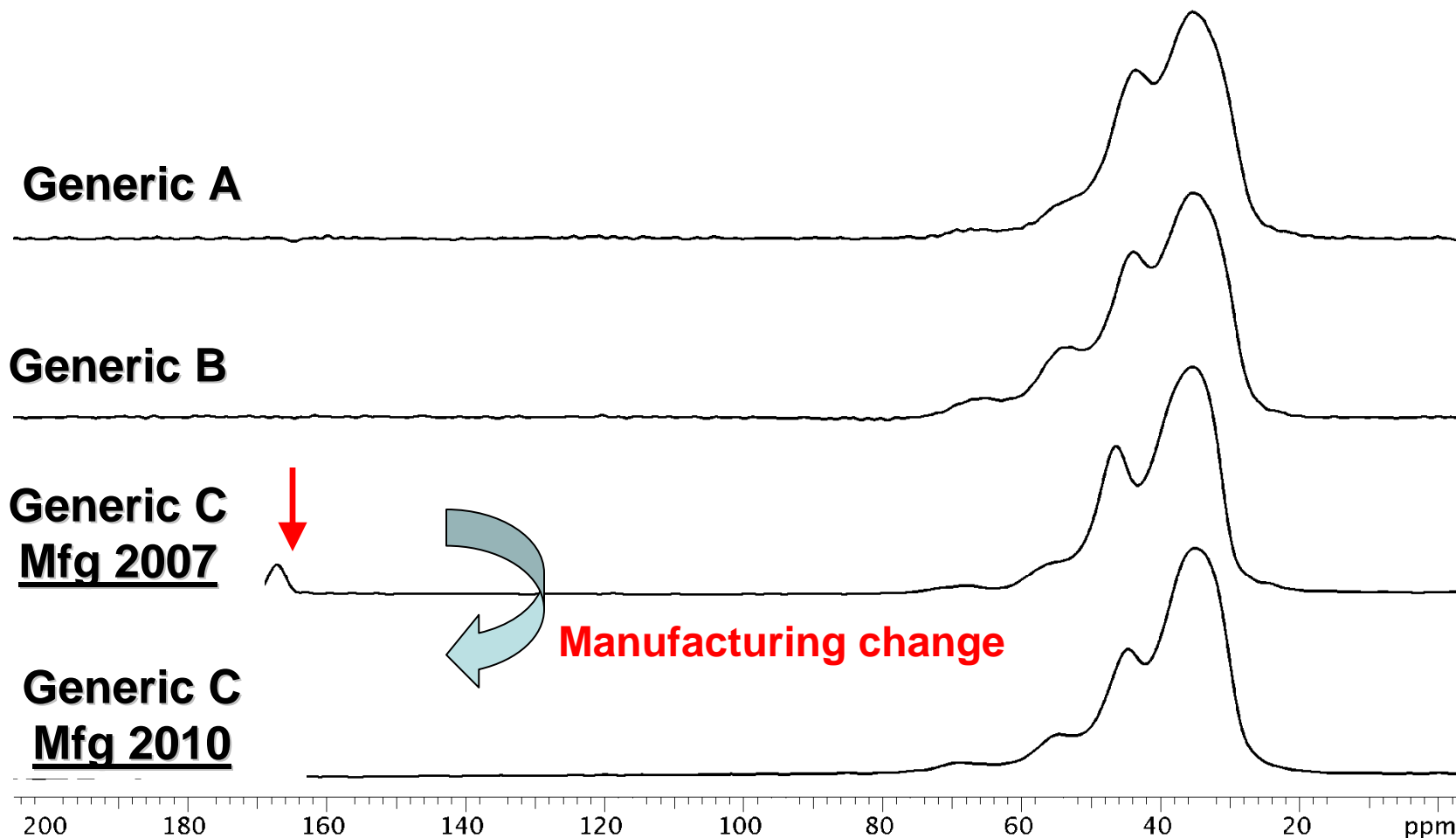


# Dissolution Profile of Eight Gabapentin Tablet Drug Products

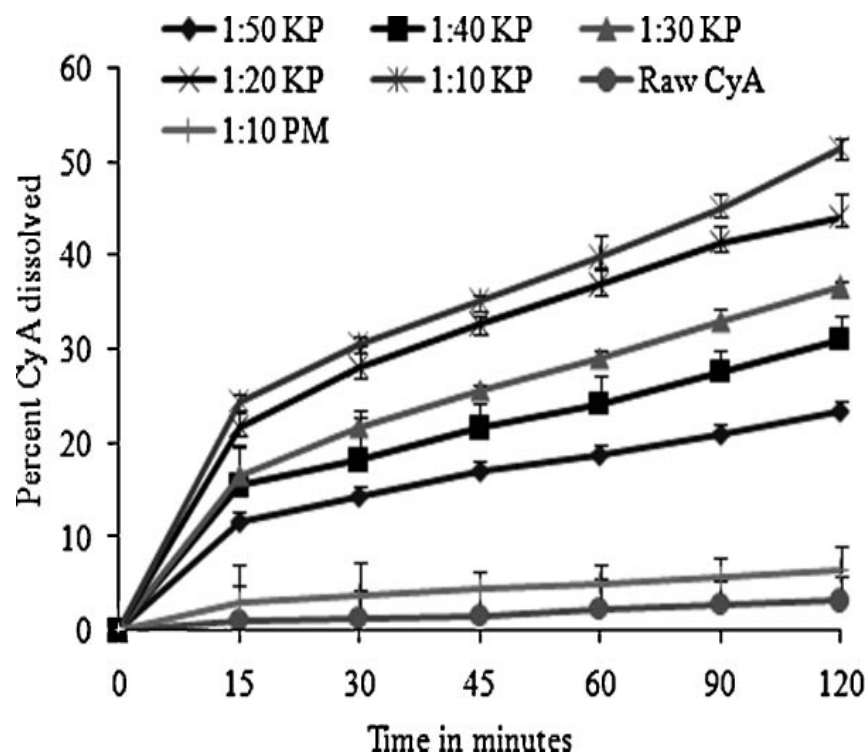
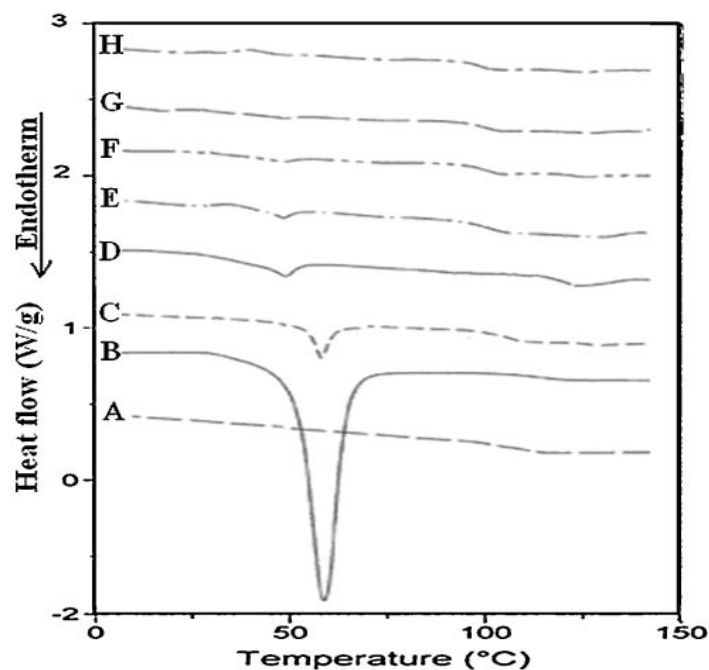


All samples met the compendial requirements of NLT 80% (Q) dissolution in 45 min

# Solid-State NMR Spectroscopy:

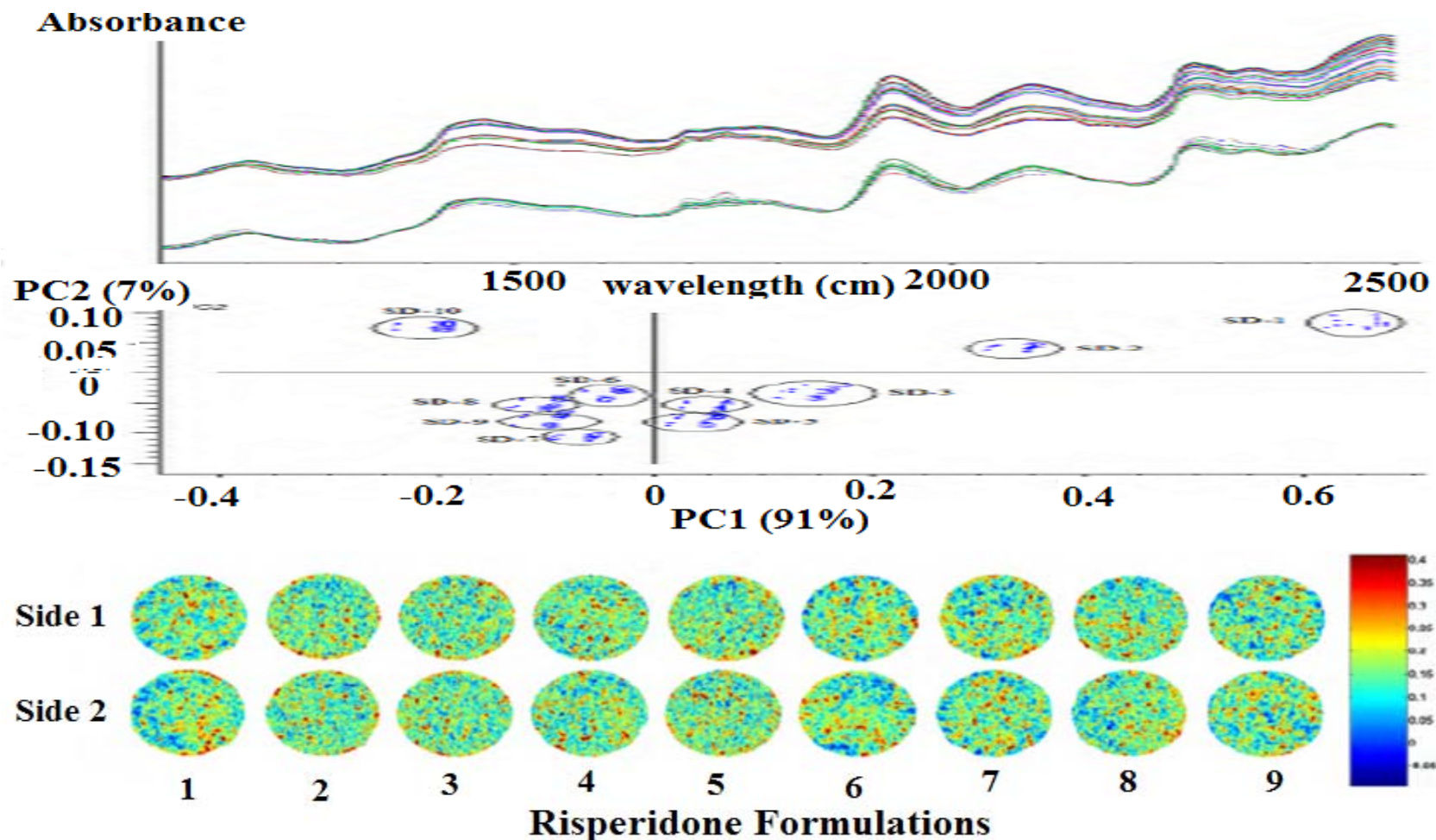


## DDS Team: DSC and Dissolution to Understand and Control Solid Dispersions



*J. Pharm., Sci., (2008), 97(12), 5328-5340*

## NIR and Chemical Imaging to Understand and Control Solid Dispersions



# pK Changes with Crystallinity

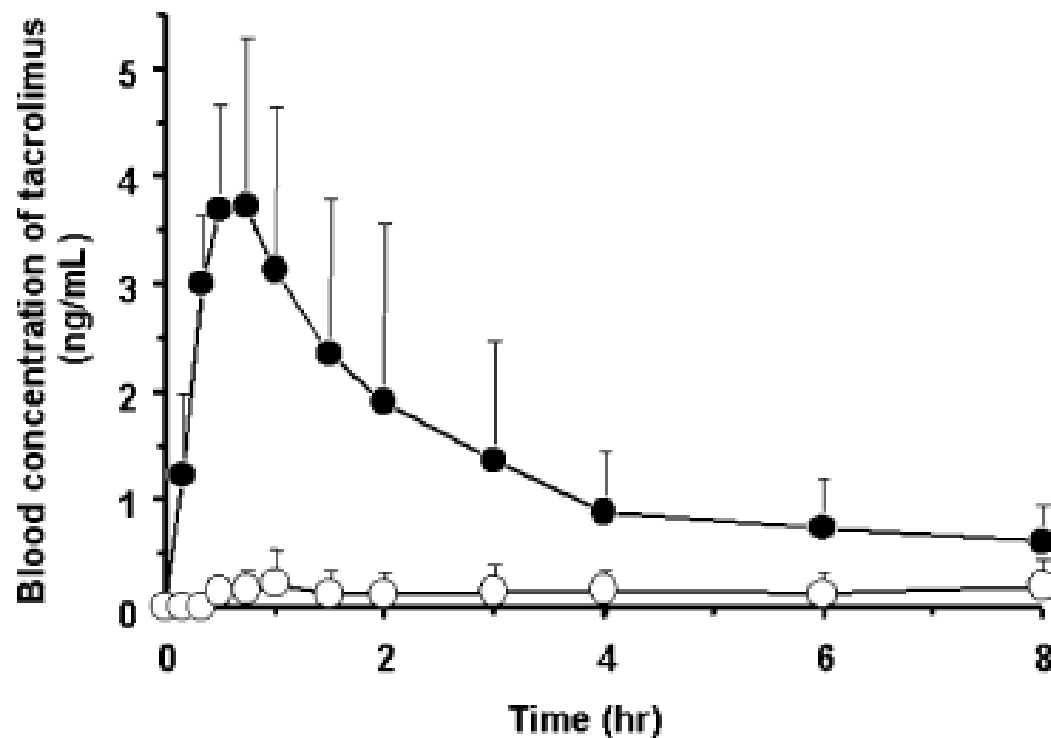


Fig. 5. Blood concentration of tacrolimus after oral administration of SDF with HPMC to beagle dogs. (●) SDF of tacrolimus with HPMC; (○) tacrolimus crystalline powders.

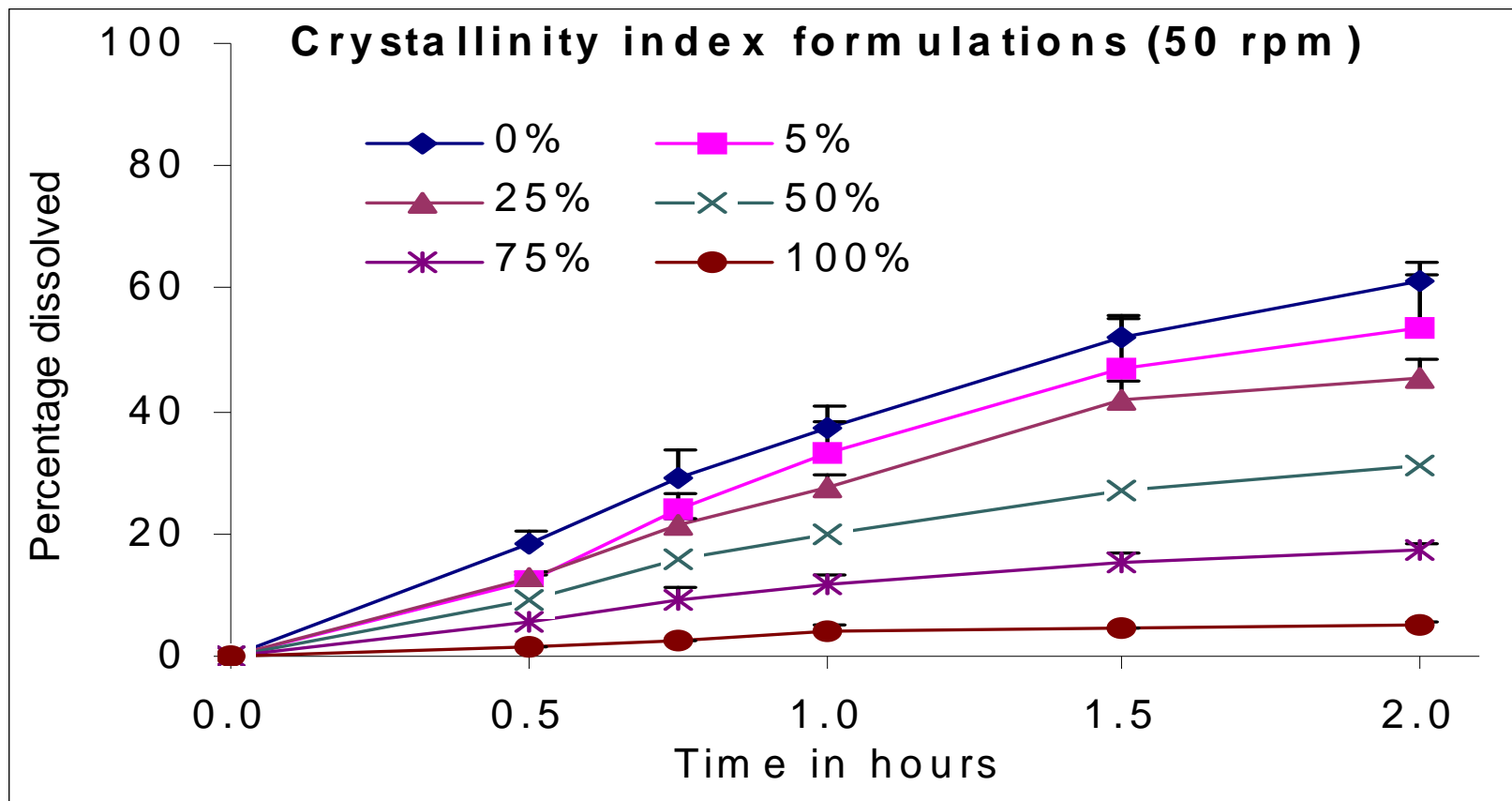
# How is Variability Explained by the Sponsor?

- Preparation method
- Drug: hypromellose ratio
- Additives and the order of addition
- Choice of solvent
- Residual solvent
- Storage condition

# Dissolution Methods in ANDA Submissions

Product 1	0.005% HPC (pH 4.5)
Product 2	0.01 m NaPO <sub>4</sub> + 0.1% SDS
Product 3	0.005% HPC (pH 4.5)
Product 4	0.005% HPC (pH 4.5)
Product 5	0.005% HPC (pH 4.5)
Product 6	0.005% HPC (pH 4.5)
Product 7	0.005% HPC (pH 4.5)
Product 8	0.005% HPC (pH 4.5)
Product 9	0.005% HPC (pH 4.5)
Product 10	0.1% SLS in 0.1N HCl (pH 4.5)

## Dissolution Data of Crystallinity Index Formulations at 50 rpm



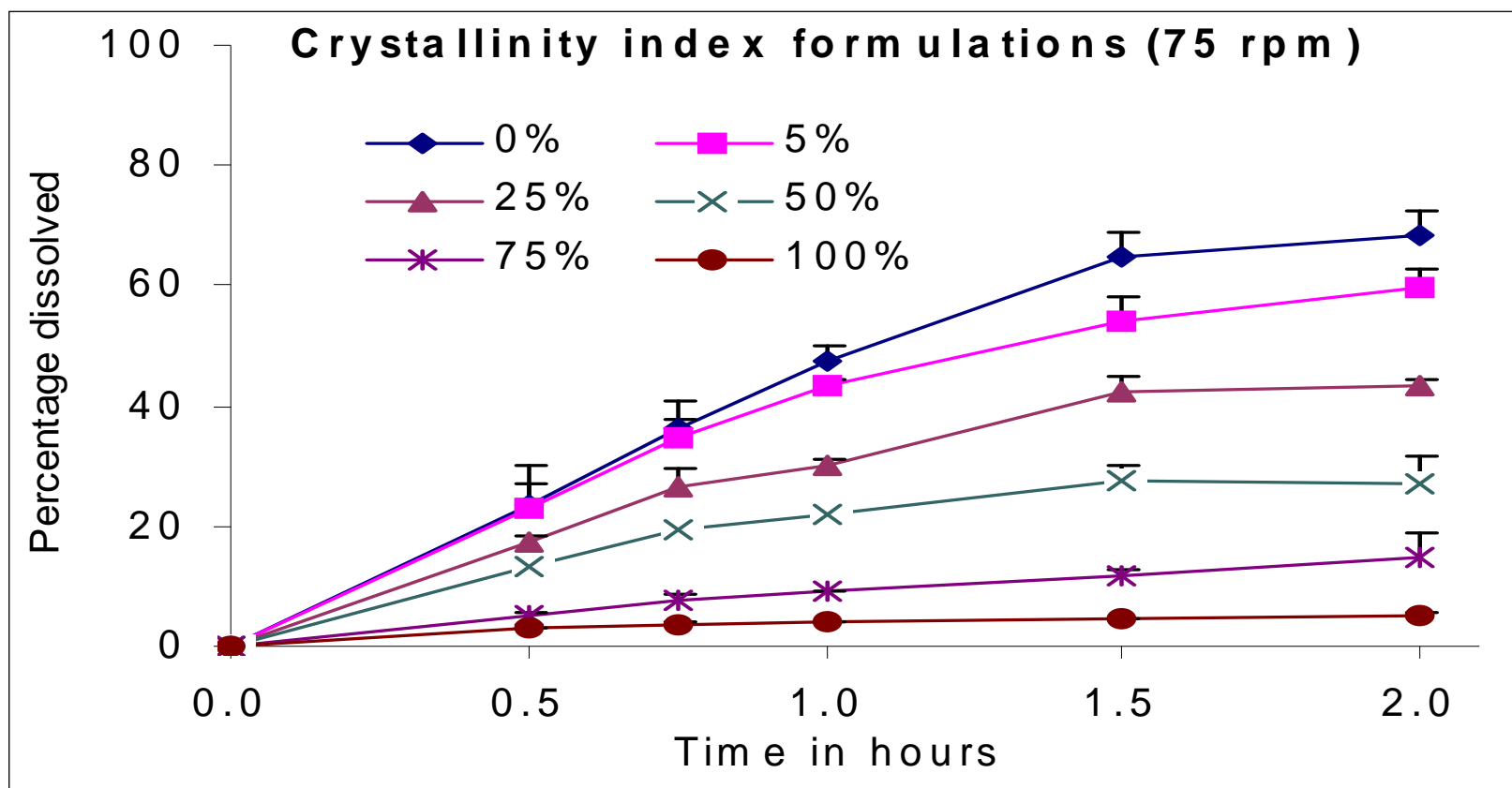
### FDA Dissolution method:

900 mL 0.002% HPC pH 4.5 with  $H_3PO_4$ , 50 rpm, 37° C

Error bars are Std. Dev. values



## Dissolution Data of Crystallinity Index Formulations at 75 rpm

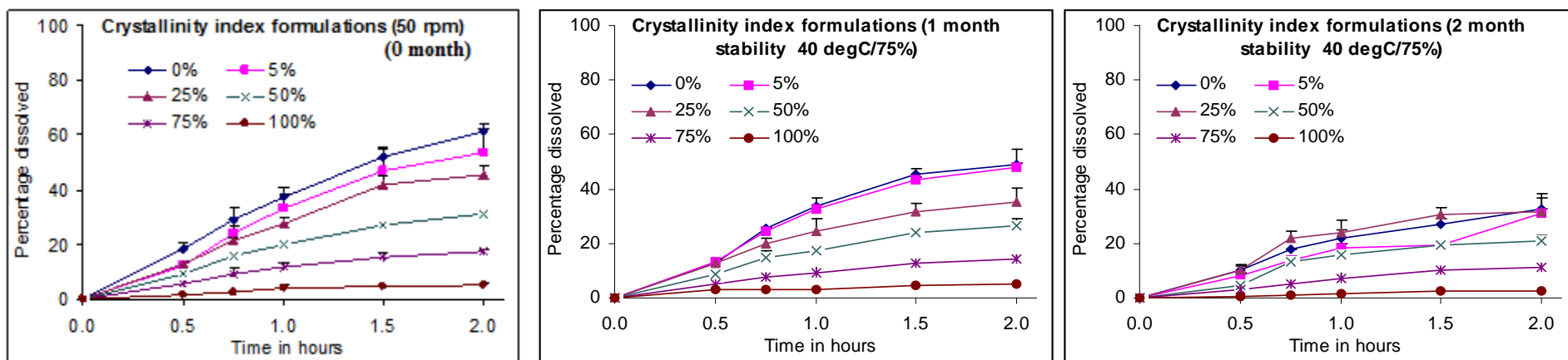


### **FDA Dissolution method:**

900 mL 0.002% HPC pH 4.5 with  $H_3PO_4$ , 75 rpm, 37° C

Error bars are Std. Dev. values

# Dissolution Data of Crystallinity Index Formulations at 0, 1 and 2 Month Stability (40deg/75%)



## FDA Dissolution method:

900 mL 0.002% HPC pH 4.5 with H3PO4

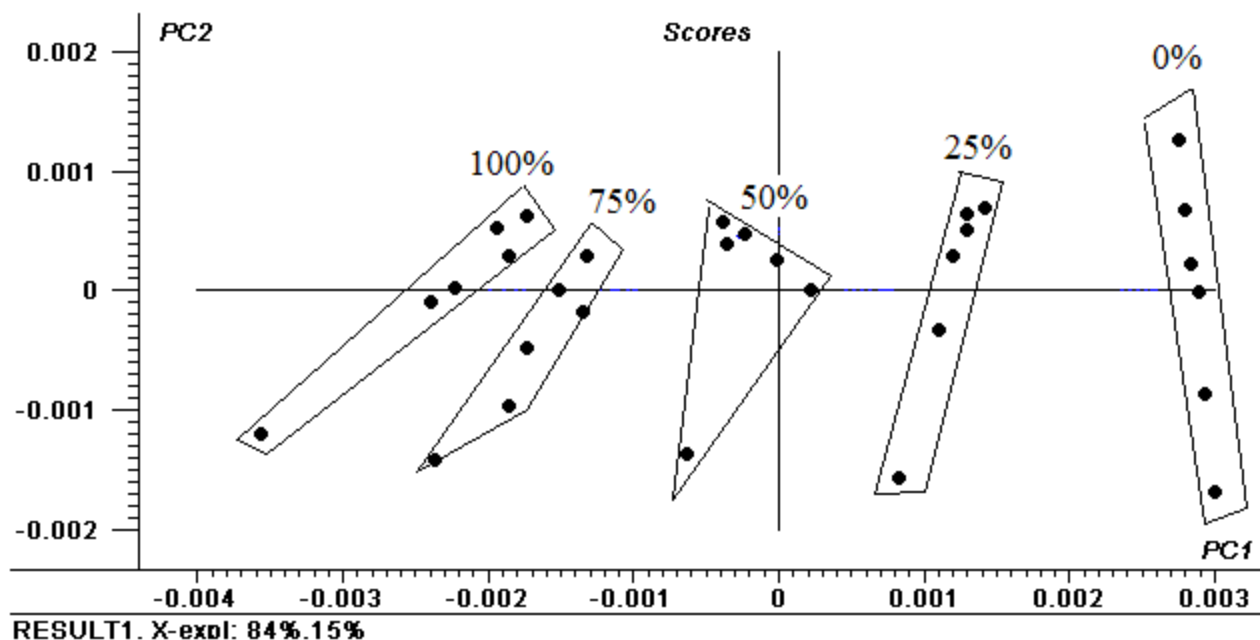
50 rpm and 75 rpm

37 degC

Apparatus II

Error bars are StDev values

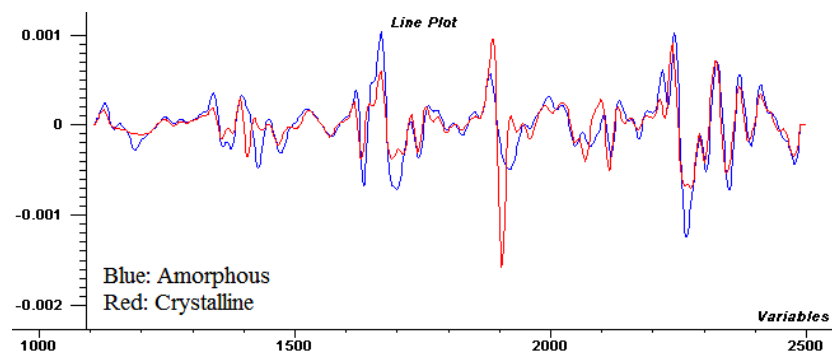
## PCA Analysis



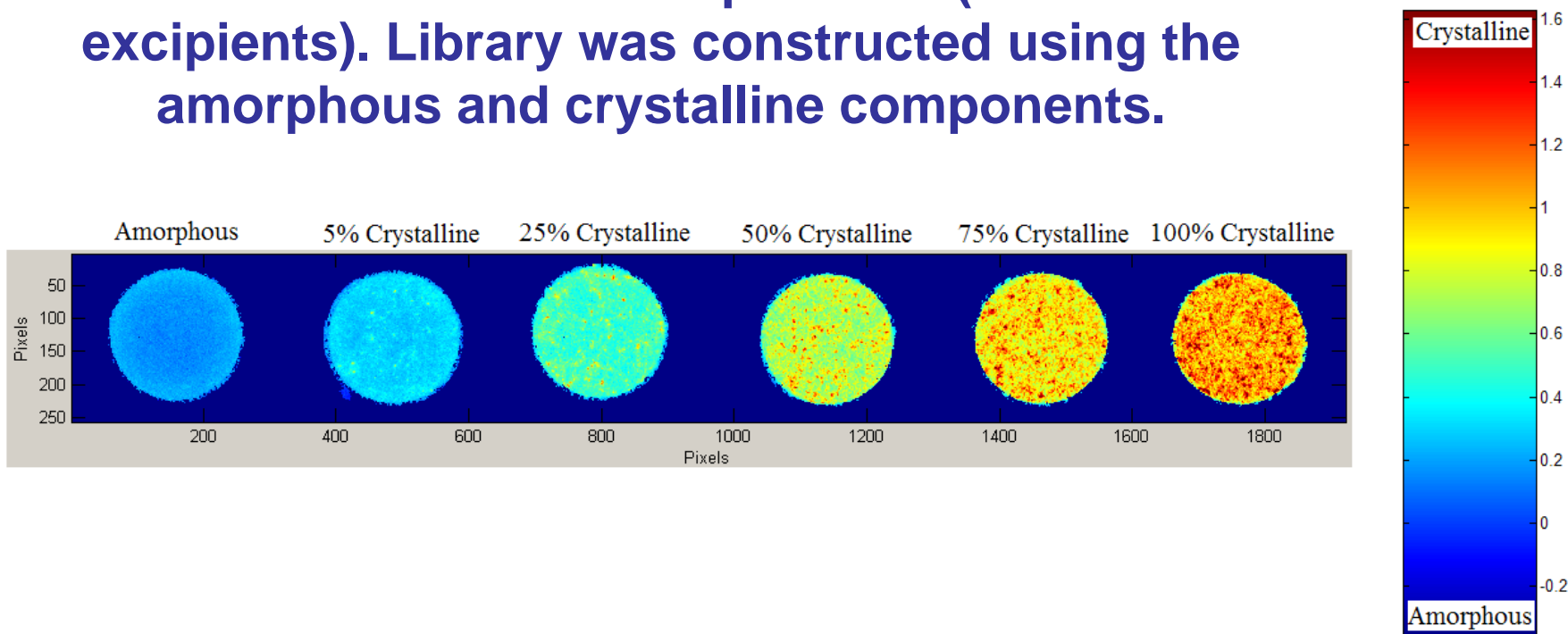
PCA analysis using full cross validation technique after processing the raw NIR data with third order polynomial Savitsky-Golay at 11 points smoothing

PC1 and PC2 explained 84% and 15% of the variability among the spectra

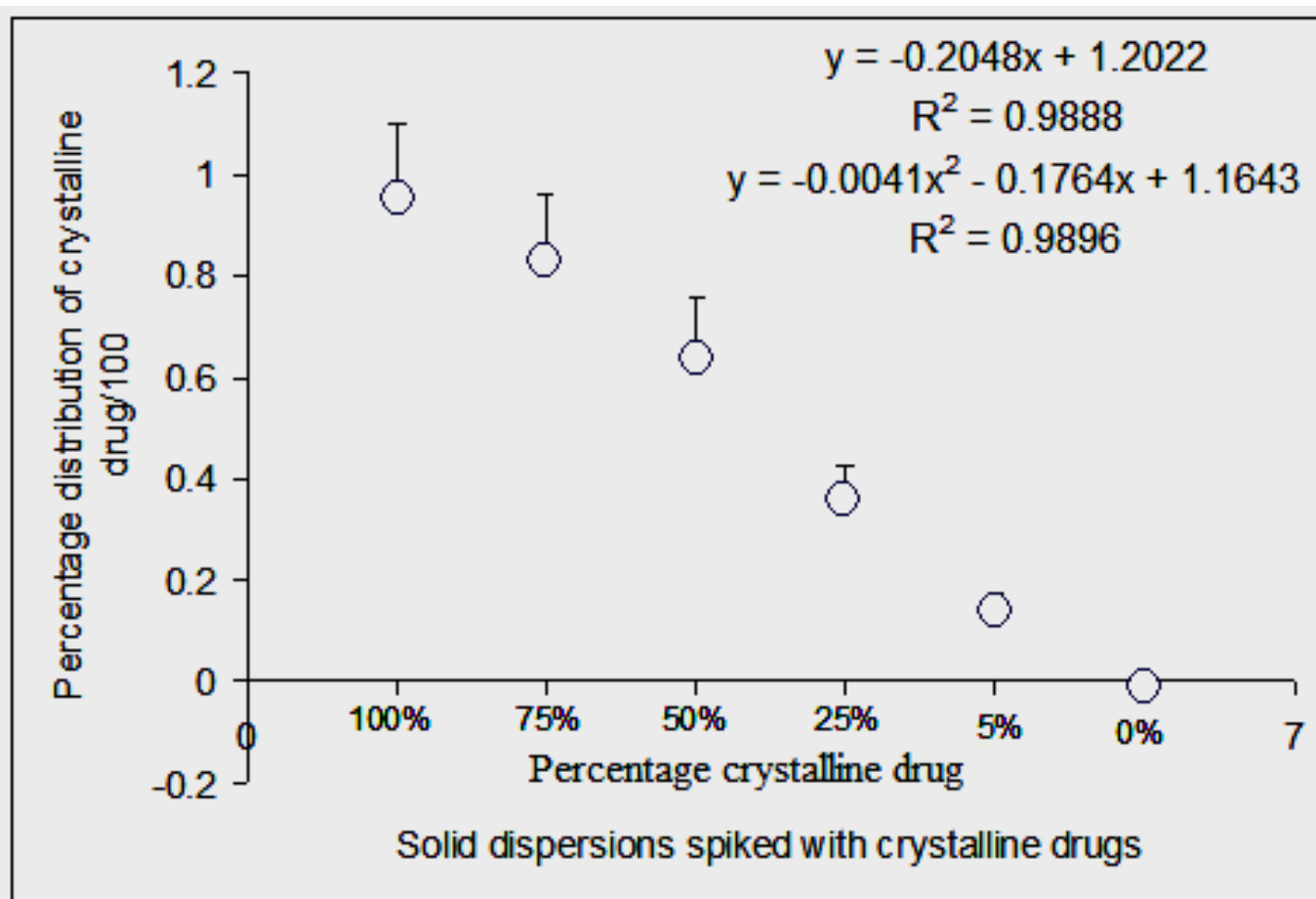
Formulations were clustered according to the degree of crystallinity for the loading vector of PC1



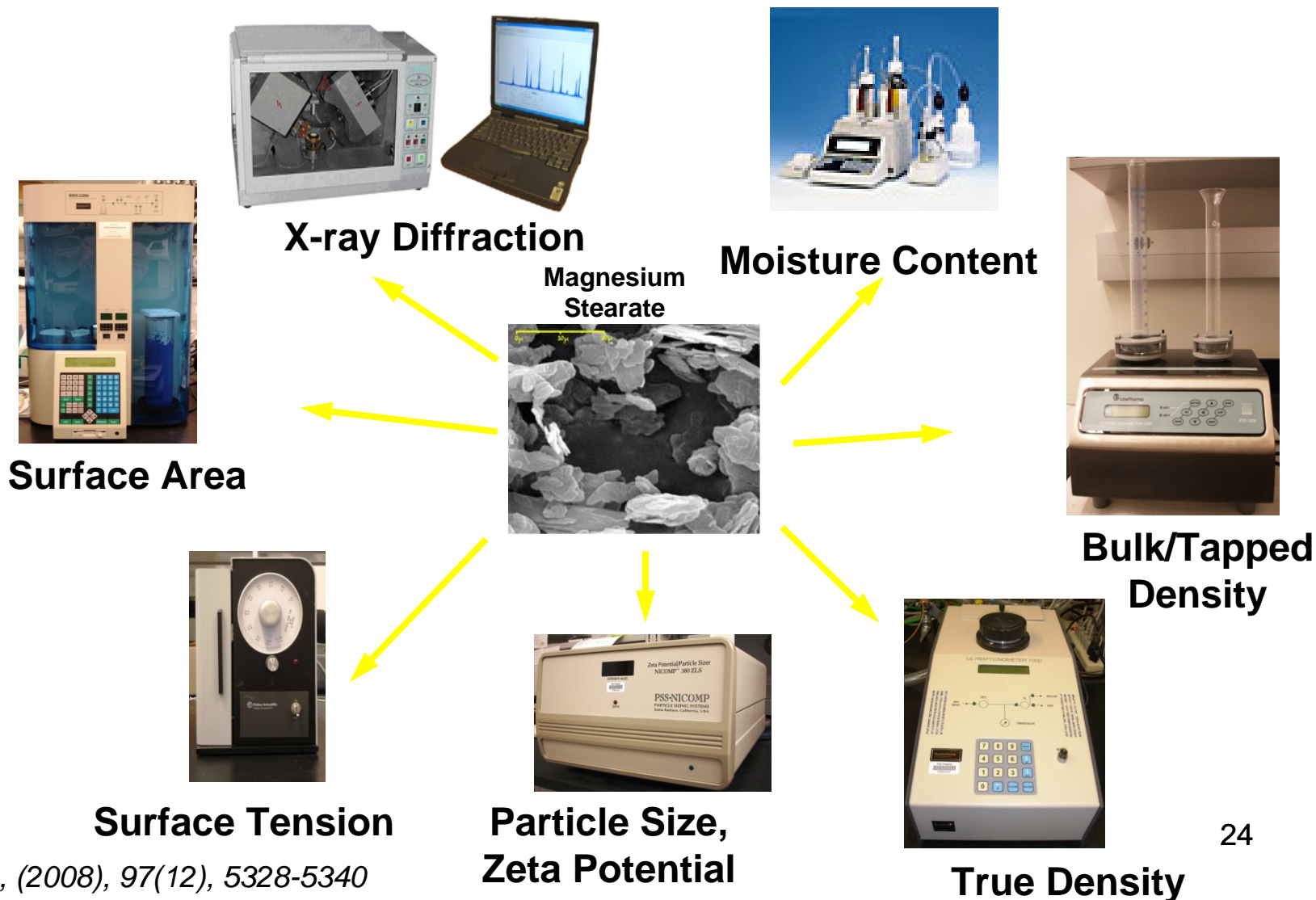
**Concatenated PLS second derivative images of tacrolimus solid dispersions (without excipients). Library was constructed using the amorphous and crystalline components.**



## NIR PLS Truncated PLS Images Statistics



# Mg.St. Bovine vs Plant Source: Raw Material Characterization



# Tablet Characterization



**Hardness  
Tester**

## Tablets



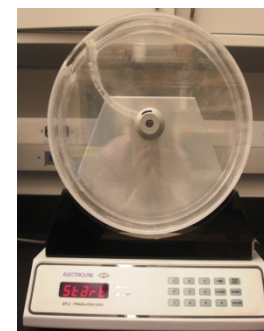
**Weight  
Measurement**



**Compression/  
Ejection Force Data**



**Dissolution Testing**

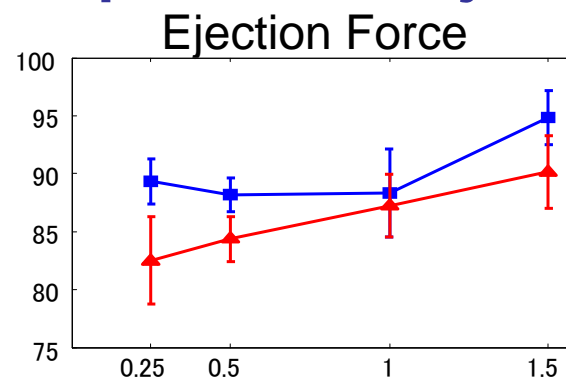
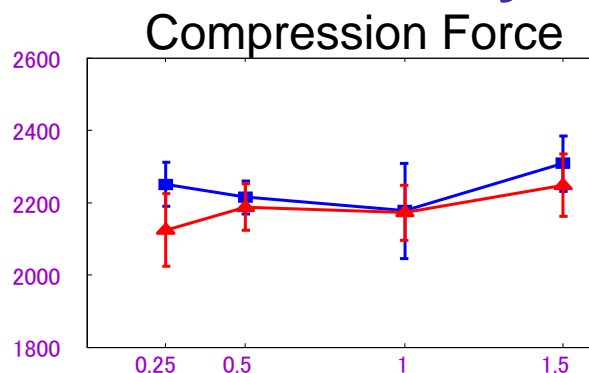


**Friability Tester**

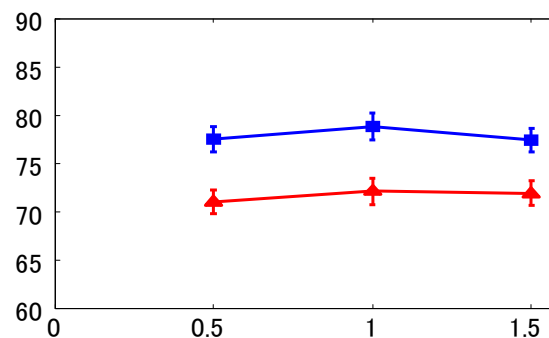
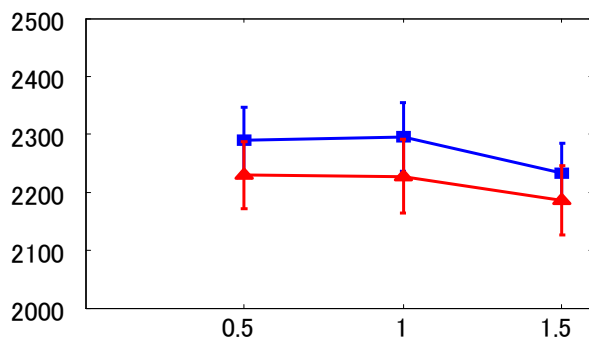


## Effects on Functionality - Compression / Ejection

Physical  
Mixture

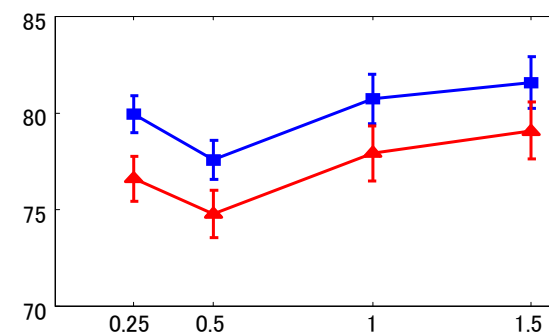
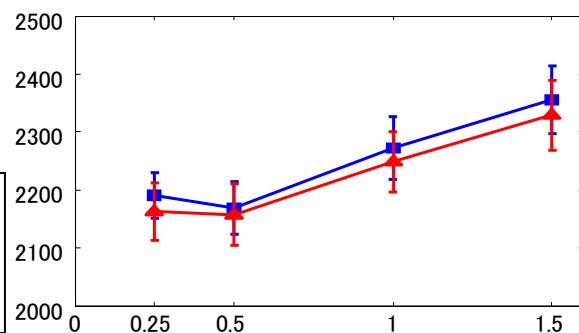


Slugging



Fluid Bed  
Granulation

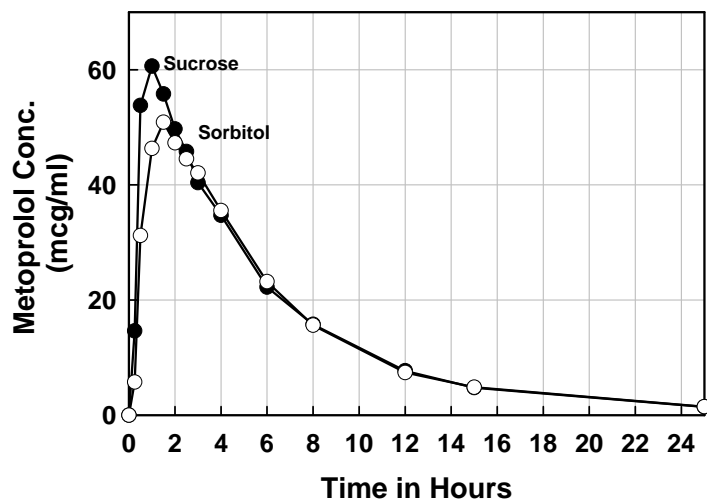
■ Bovine MgS  
▲ Vegetable MgS



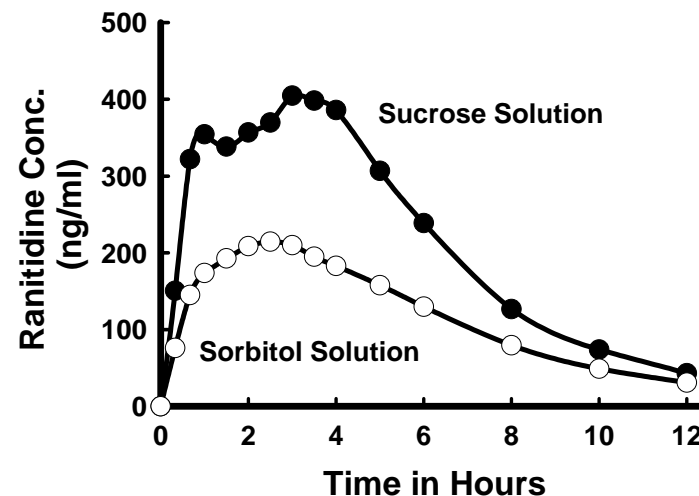


# Biopharmaceutics Team: BCS Guidance-Excipient Effect

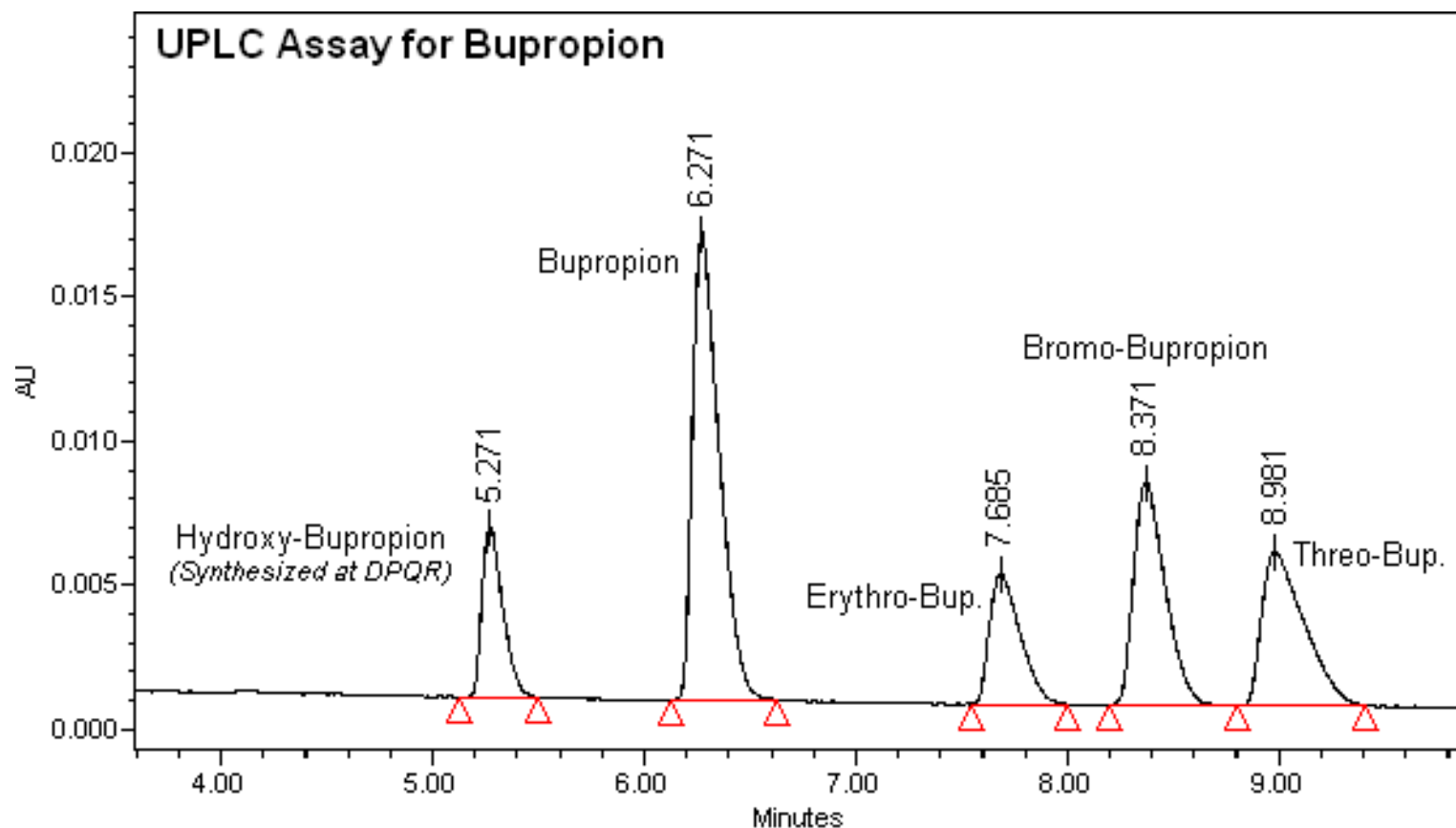
**BCS Class I-Drug**



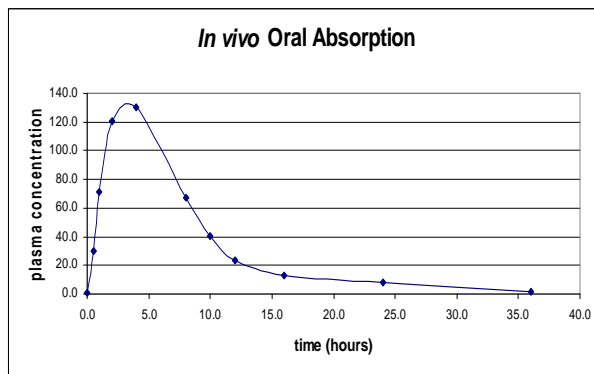
**BCS Class III-Drug**



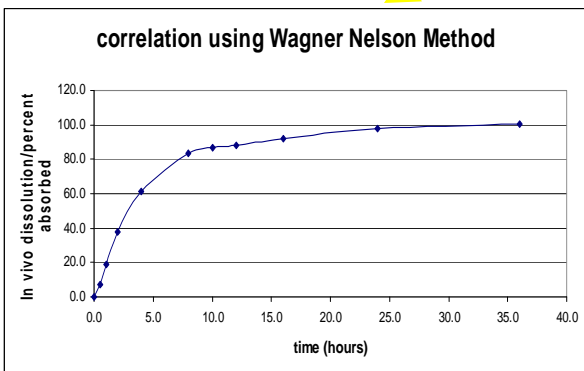
# Bupropion Bioequivalence Studies (ongoing)



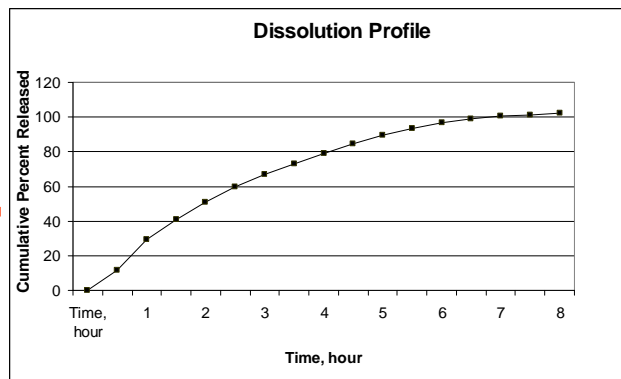
# Setting Dissolution Specifications?



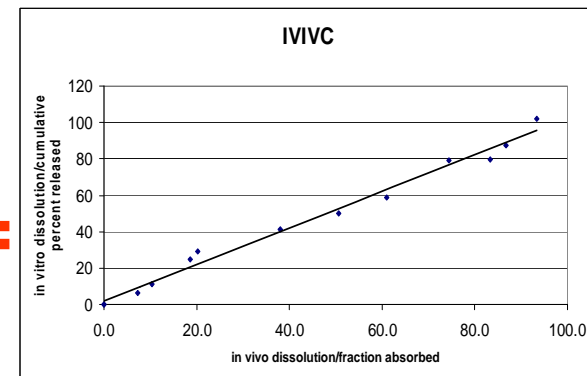
Deconvolution



+



=



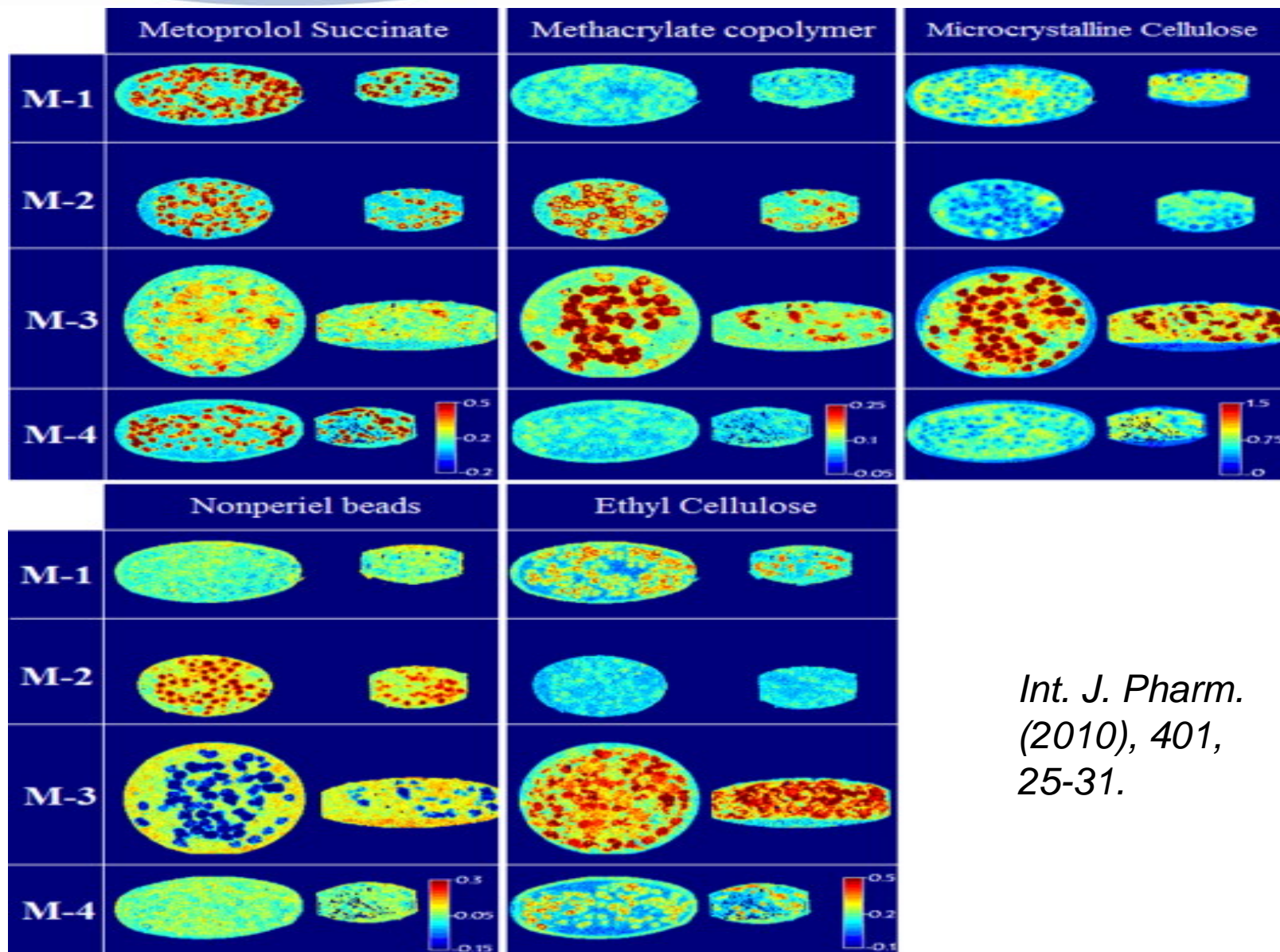


# Tablet Splitting - Influence of Tablet Splitter

600 mg gabapentin tablets from same bottle







*Int. J. Pharm.*  
(2010), 401,  
25-31.

# Conclusions

DPQR scientists continues to provide regulatory research support to the Office of Generic Drugs

# Acknowledgements

DPQR staff

OTR office support

Financial support from NIH, MCM, CP, OPS, OGD, OWH, ONDQA, OC, RSR

# **Impact of Formulation and Quality on Safety and Acceptance of Generic Drugs**

Advisory Committee for Pharmaceutical Science and Clinical Pharmacology

Gordon Johnston, R.Ph., M.S.

Generic Pharmaceutical Association

July 26, 2011

# Outline

- Overview of generic drug quality standard
- Formulation considerations
- Quality by Design
- Literature
- Summary

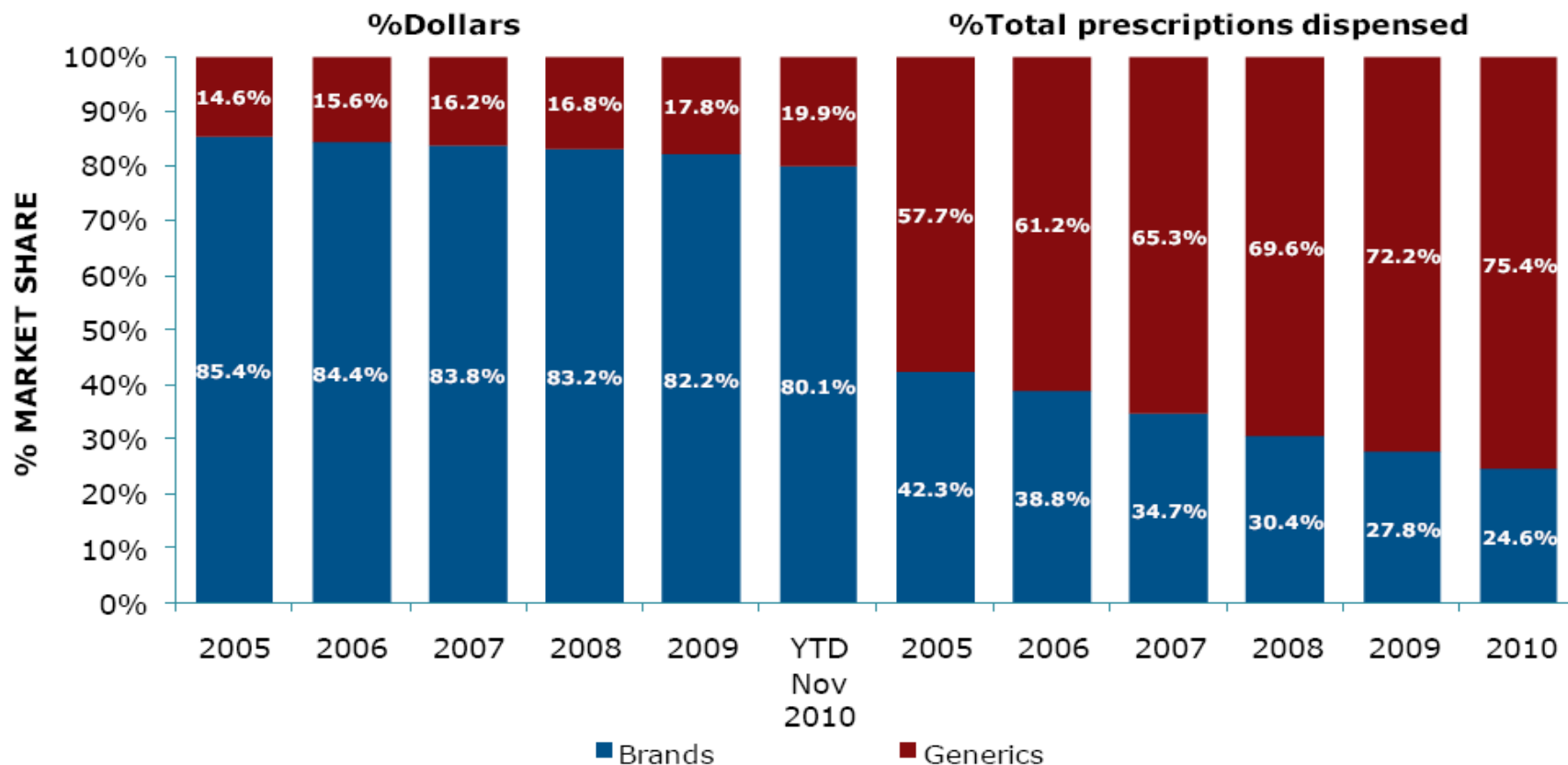


# Why Are We Having This Dialogue?

- 27 history of generic drugs in the U.S.
- Anecdotal reports of quality concerns
- Misconceptions about quality standards and FDA requirements for generic drugs



# Sales and TRx share brands and generics

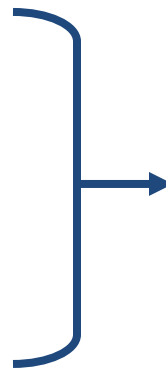


Source: IMS Health, National Sales Perspectives, Nov 2010, Branded generics disaggregated, Source: IMS Health, National Prescription Audit, Branded generics disaggregated, Dec 2010

# FDA Approval Criteria

## NDA vs. ANDA

- Chemistry
- Manufacturing
- Controls
- Labeling
- Testing
- Bioequivalence (Bioavailability)
- Animal Studies
- Clinical Trials



- Chemistry
- Manufacturing
- Controls
- Labeling
- Testing
- Bioequivalence

# Generic Drug Approval Requirements

- Same quality requirements
- Same manufacturing requirements
- Same labeling as brand product
- Same safety and efficacy, i.e., therapeutic equivalence

# Generic Formulations

## Pharmaceutical Equivalence

- ☐ Same active ingredient
- ☐ Same strength
- ☐ Same dosage form
- ☐ Same route of administration
- ☐ Comparable labeling



## Bioequivalence

- ☐ In Vivo Studies
  - PK
  - PD
  - Clinical
- ☐ In vitro Studies



## Therapeutic Equivalence

**"A" Therapeutic  
Rating  
(A substitute)**

# Inactive Ingredients

- Generic formulations **MUST** use inactive ingredients previously approved in a drug product for the same route of administration
- Cannot exceed the quantities previously approved for same route of administration (based on single dose or total daily exposure)
- Meet compendial or other applicable standards of quality, purity, and identity

# Specifications

- Drug product specifications are based on established standards. Typically required to reflect the tightest standard based on:
  - Process capabilities
  - ICH
  - USP
  - Reference listed drug
- Specifications are set to assure quality throughout the shelf life of a product

# Quality Standards

- Product Quality Standards
  - USP
  - ICH
  - Reference listed drug
  - EP, JP
- All inactive and active ingredients must be national and/or international standards of quality



# Quality Standards

- Good Manufacturing Practices
  - Generic facilities are subject to FDA's requirements for good manufacturing practices
  - Inspected with the same frequency as brand facilities

# ANDA Review Process

- Generic drug review cadre represent a mix of highly trained experts
  - Chemists
  - Process engineers
  - Pharmacokineticists
  - Pharmacologists
  - Physicians
  - Pharmacists
- Same relevant training and expertise as New Drugs

# Post Approval Requirements

- FDA has a single, consistent standard for monitoring drug product quality after approval
- Generic manufacturers must review, test and report on drug product quality following the same regulations as brand products

# Quality by Design: A Transition in the Approach to Drug Product Development

# Quality by Design

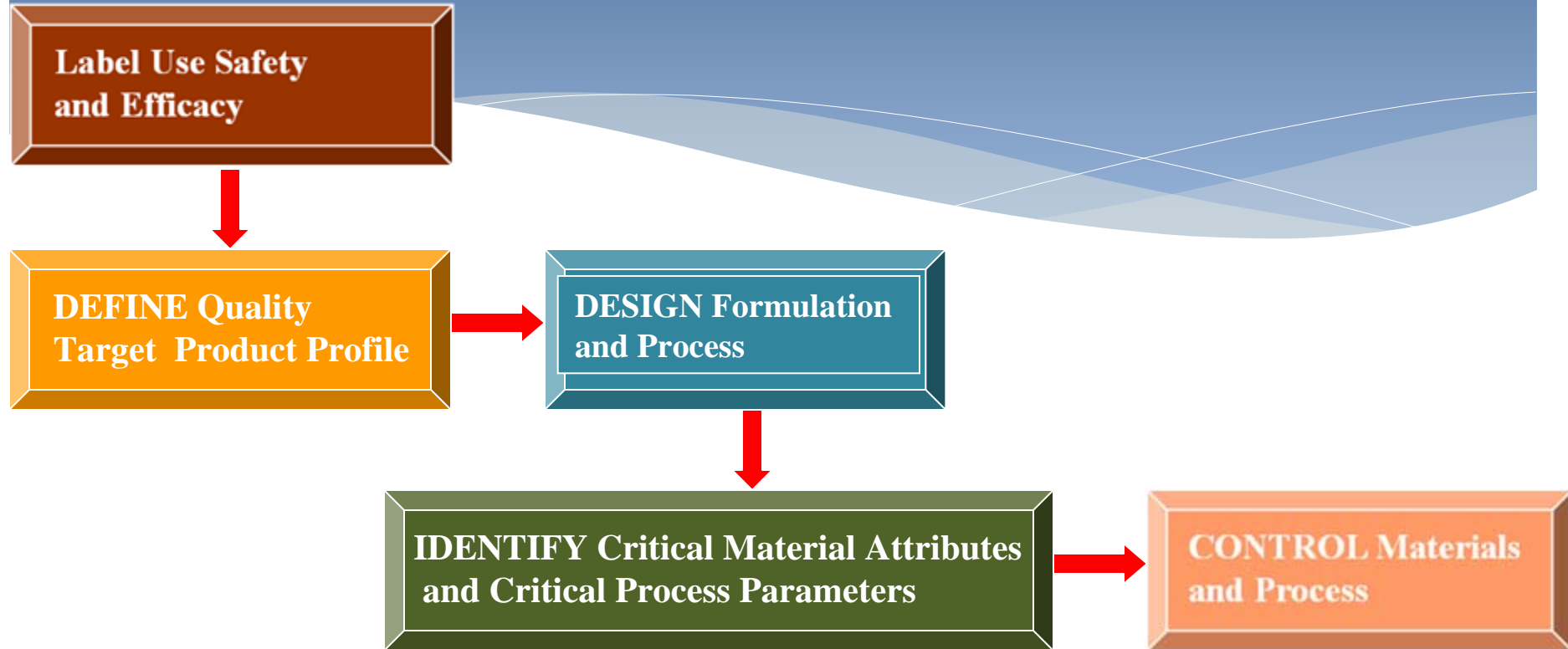
- \*A systematic approach to development that begins with pre-defined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.
- \* Industry has historically employed QbD principles
- \*FDA's QbD initiative represents an advancement in regulatory science to provide a more consistent and defined approach to formulation development

# An Integrated Approach to Product/Process Design

\*Helen Winkle- May 5, 2011



# Overview of QbD



**TARGET**

**DESIGN and  
UNDERSTANDING**

**IMPLEMENTATION**

# Goals of QbD\*

- Designing quality into all aspects of drug development
- Ensuring manufacturers are responsible for quality of products
- QbD is [in accordance with Q8(R)]:
  - Systematic approach to development
  - Begins with predefined objectives
  - Emphasizes product and process understanding and process control
  - Based on sound science and quality risk management
- Change in how FDA will look at applications - assessment focused on critical quality attributes (chemistry, pharmaceutical formulation, and manufacturing processes) as relate to product performance

\* H Winkle, FDA, May 5, 2011



# Required Elements of QbD for Generic Drugs

- Quality target product profile (QTPP)
  - Including critical quality attributes (CQAs) of the drug product
- Product design and understanding
  - Critical material attributes (CMAs) of the drug substance and excipients
- Process design and understanding
  - Critical process parameters (CPPs)
- Control strategy
  - How and why

# Factors that Impact Product Quality and Performance

- Formulation
- Quality of API and excipients
  - Impurities
  - Physical form
- Storage conditions

# Prior Knowledge

- Industry should be allowed to apply extensive commercial manufacturing experience
- Example: Injectable manufacturing plants utilize a fixed number of well understood terminal sterilization cycles
  - Adopting a suitable existing cycle is the appropriate application of prior knowledge
  - Utilizing existing cycles promotes plant efficiency
  - Re-inventing the wheel or proving the negative provides no value to manufacturer or consumer

# Questions Remain

- Adoption of QbD for active ingredient manufactures
- Use of prior knowledge
- Stability requirements at the time of filing
- Number of batches/size of batches at the time of filing
- How to address scientific disagreements

# QbD and the Manufacture of APIs

- Principles of QbD are not limited to FDF
- What are the agency's expectations for APIs?
  - Implementation timeline
  - Data requirements

# Quality Target Product Profile

- The development goal is to be interchangeable with the brand, i.e. generic
- Not the same as NCE product development
- A justification of therapeutic equivalence should be sufficient for most parameters

QTPP Element		Target	Justification
Dosage form		Tablet	Comparable size, differences in shape and color acceptable
Dosage design		IR tablet	Pharmaceutical equivalent to the brand
Route of Administration		Oral	Pharmaceutical equivalent to the brand
Dosage strength		20 mg	Pharmaceutical equivalent to the brand
Container/closure system		HDPE bottle and cap	Provide 24 month of shelf life
Pharmacokinetics		AUC and Tmax profile BE to brand	Obtain 'A' rating
Drug product quality		Meet compendial standards, ICH standards and quality parameters established by the brand	
	Physical Attributes		
	Identification		
	Potency		
	Content uniformity		
	Impurities		
	Residual solvents		
	Dissolution		
	Microbial limits		
	Hardness		
	Friability		
Stability		24 RT temperature shelf life	Market demand upon commercialization

# Generic Drug Safety and Performance

# Ongoing FDA Support of Bioequivalence Standards





# Generic Drug Bioequivalence Studies

- 1997 study of 127 bioequivalence studies
  - Mean difference between brand and generic
    - AUC = 3.47%
    - Cmax = 4.29%
- 1984-1986 study of 224 bioequivalence studies
  - Mean difference between brand and generic
    - AUC = 3.5%
- 2009 study of 2,070 bioequivalence studies performed between 1996-2007
  - Mean difference between brand and generic
    - AUC = 2.3%

## Original article

# Acute epilepsy exacerbations in patients switched between A-rated anti-epileptic drugs

### Conclusions:

After addressing potential confounders, no evidence that A-rated switching was associated with increased acute exacerbations of epilepsy was found. Study limitations include potentially incomplete identification of seizures, no information on indication for medication use, and limited information on duration and severity of disease. This study provides additional insight into the relationship between A-rated AED switching and acute exacerbations of epilepsy.

# Clinical Equivalence of Generic and Brand-Name Drugs Used in Cardiovascular Disease

A Systematic Review and Meta-analysis

**Conclusions** Whereas evidence does not support the notion that brand-name drugs used in cardiovascular disease are superior to generic drugs, a substantial number of editorials counsel against the interchangeability of generic drugs.

*JAMA.* 2008;300(21):2514-2526

[www.jama.com](http://www.jama.com)

## Original article

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## **Observational cohort study of switching warfarin sodium products in a managed care organization**

CLAUDIA N. SWENSON AND GRODZANA FUNDAC

“Conclusion... Use of a generic warfarin sodium product...in patients previously receiving the innovator product...did not change the International Normalized Ratios more than did continued use of the innovator product...”

## Seizure Outcomes Following the Use of Generic versus Brand-Name Antiepileptic Drugs

### A Systematic Review and Meta-Analysis

Aaron S. Kesselheim,<sup>1</sup> Margaret R. Stedman,<sup>1</sup> Ellen J. Bubrick,<sup>2</sup> Joshua J. Gagne,<sup>1</sup>  
Alexander S. Misono,<sup>1</sup> Joy L. Lee,<sup>1</sup> M. Alan Brookhart,<sup>3</sup> Jerry Avorn<sup>1</sup> and William H. Shrank<sup>1</sup>

### Conclusion

A systematic review and meta-analysis of trials comparing seizure outcomes from use of brand-name and generic AEDs shows no association between loss of seizure control and generic substitution for at least three types of AEDs. Observational study data suggest that brand-name-to-generic AED switching may be associated with 'switch-backs' and increased rates of health services utilization, but these studies are limited by unmeasured confounders and other factors in their design. Although physicians may want to consider more intensive monitoring of high-risk patients taking AEDs when any medication change occurs, in the absence of better data, there is little evidence-based rationale to challenge the implementation of generic substitution for AEDs in most cases.

Conclusion... there is little evidence based rationale to challenge the implementation of generic substitution for AEDs in most cases.”

## Consumers' Views on Generic Medications

Caroline A. Gaither, Duane M. Kirking, Frank J. Ascione, and Lynda S. Welage

J Am Pharm Assoc 41(5):729-736, 2001. © 2001 American Pharmaceutical Association

**Conclusion:** More research is needed on consumers' decision-making processes and behaviors regarding generic medications. Mass education efforts, financial incentives, and greater communication among patients and health care professionals should continue to influence the use of generic medications.



## **Discontinuation Rates and Healthcare Costs in Patients Starting Brand and Generic Sertraline**

**Anna Vlahiotis, MA; Scott Devine, PhD, MPH; Jeff Eichholz, PharmD; Adam Kautzner, PharmD**

**Presented at the  
2010 Academy of Managed Care Pharmacy Educational Conference, October 15, 2010, Saint Louis, MO**

“Conclusions: The risk of discontinuation and the short-term healthcare costs were lower in patients starting generic sertraline compared with patients starting the branded





## **Discontinuation Rates and Healthcare Costs in Patients Starting Brand and Generic SSRIs and SNRIs**

**Anna Vlahiotis, MA; Scott Devine, MPH, PhD; Jeff Eichholz, PharmD; Adam Kautzner, PharmD**

**Presented at the  
2010 Academy of Managed Care Pharmacy Educational Conference, October 15, 2010, Saint Louis, MO**

“Conclusions: The risk of discontinuation was similar in patients starting either a branded or a generic SSRI/SNRI... The results of this study provide further evidence that the use of generic antidepressants as first-line agents in the treatment of some mental health disorders can be encouraged as an important pharmacy cost saving approach.”

# Summary

- The regulatory structure for generic drugs is designed to assure quality
- FDA scientists apply the same quality standards to brand and generic drugs
- Regulatory science advances/QbD the next step to underscore quality
- Long history of generic drug safety , therapeutic equivalence, patient acceptance